DISEASES of the CHEST

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Mediastinal Tumors and Cysts in the Adult*

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During the years 1932 to 1957, 117 patients with proved mediastinal tumors or cysts were treated by the Thoracic Surgical Service of the Veterans Administration Hospital, Hines, Illinois.

Except for one woman, the group consisted of adult men between the ages of 21 and 70. At the outset, it becomes apparent that our percentages as to types of lesions will differ from other reported series — such as the findings of Peabody.[1] Previously documented series have shown that up to 36 per cent of the group harboring such lesions were women. Another investigator reported 20 per cent of his mediastinal tumors were found in children.

It is our purpose to show that early thoracotomy after adequate diagnosis is the treatment of choice in these lesions. The adequacy of preoperative diagnosis has been enhanced, in recent years, by both scalene node biopsy and angiocardiogram. Scalene node biopsy has been particularly useful in diagnosing lymphomas, granulomas and carcinomata.

In keeping with the majority of authors on this subject, the following lesions are excluded from this study: (1) Carcinoma of the esophagus; (2) Metastases or mediastinal extension of any pulmonary carcinoma; and (3) Metastases of the mediastinum from any other primary tumor in the body.

TABLE 1

	No. Cases	Per cent of Series
Cysts	22	20 per cent
Neurogenic Tumors	5	4 per cent
Lymphomas	16	13 per cent
Intrathoracic Thyroid	15	13 per cent
Intrathoracic Parathyroid	1	1 per cent
Thymoma	5	4 per cent
Mesenchymal	27	23 per cent
Teratomas	11	10 per cent
Carcinomas	6	5 per cent
Miscellaneous	5	4 per cent
Vascular	4	3 per cent
	117	100 per cent

Cysts

Twenty-two patients, excluding cystic teratomas (dermoid cysts) were treated.

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Bronchogenic Cysts

Until 1952, less than 100 bronchogenic cysts had been described. However, these tumors are much more common than had been realized. Bronchogenic cysts made up 14 per cent of our entire series.

These cysts are usually thin-walled and occur in the posterior portion of the superior mediastinum at the level of the coryna. Maier[2] has classified them into four groups on the basis of their location; paratracheal, corynal, hilar and paraesophageal.

Hirschfield[3] stated that up to 60 per cent of these cysts were symptomatic. Only two of our 16 cases (12.5 per cent) were discovered on routine chest x-ray films, the other 14 were symptomatic.

Pericardial Cysts

Pericardial cysts are rare — perhaps it is better to say they are rarely reported. Less than 100 have been described. Usually these patients are asymptomatic; however, two of our four cases had complaints referable to the thorax.

These cysts are usually situated anteriorly and lie in the cardiophrenic angle to either side, more commonly on the right. Pericardial cysts may be formed due to the failure of primitive coelomic lacunae to fuse.

Enterogenous Cysts

The most common site of these cysts is in the posterior mediastinum close to the hilus from where the cyst usually expands into either chest cavity. There is still debate as to the exact mechanism of origin.

Neurogenic Tumors

The roentgenographic appearance of primary nerve tumors is probably more characteristic than any other group of mediastinal tumors. These neoplasms are almost universally situated in the posterior mediastinum, showing an oval or rounded appearance with a smooth or scalloped border. Bone erosion and dumbbell penetration into the inter-

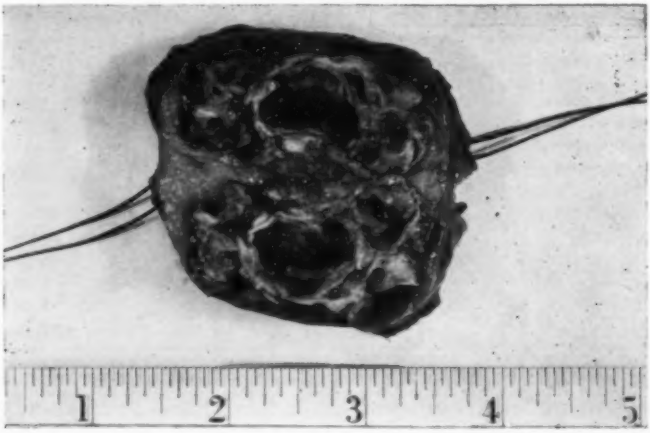

FIGURE 1: Teratoma removed from right superior mediastinum of a 60 year old white man. He had vague chest complaints for five years before admission.

vertebral foramina are common. In comparison with every other series, our percentage of neurogenic tumors was remarkably small. (4 per cent).

True neurofibromas arise from all elements of the nerve trunk; the perineurium, endoneurium, connective tissue as well as the axons and sheath cells. Neurilemmomas arise from the sheath of Schwann.

Lymphomas

Lymphomas accounted for 13 per cent of our entire series. This percentage places our findings midway between Nelson[4] (23 per cent) and Ringertz[5] (3.2 per cent) series. Our cases were all considered to be primary in the mediastinum.

In addtion to other evidences of the disease, such as superficial lymphadenopathy, a lateral x-ray film reveals a rather distinctive infiltration in the anterior mediastinum. This area is a thin, plaque-like induration of indefinite borders. This finding together with a portero-anterior film showing widening of the mediastinum is enough to suggest the diagnosis.

Lymphosarcoma originating in the mediastinum is seldom found and rarely proved. All four of our cases were proved microscopically.

Three cases were diagnosed microscopically as lymphoblastoma. All three tumors were shown to originate in the mediastinum and remained limited to this region. Hodgkin's disease which is limited to the mediastinum is also uncommon.[6] This disease was formerly diffiicult — if not impossible — to diagnose without thoracotomy. Scalene node biopsy has been of such value that the "radiation test dose" procedure has been practically abandoned — as well it should.

Substernal Thyroid

Less than 1 per cent of thyroid disease is found to be substernal. Clute and Lawrence[7] classify these goiters as those which extend below the arch of the aorta. They believe that 1 to 10 per cent of goiters are intrathoracic and that if the substernal, retrosternal and subclavicular goiters are included the figure would be between 10 and 30 per cent.

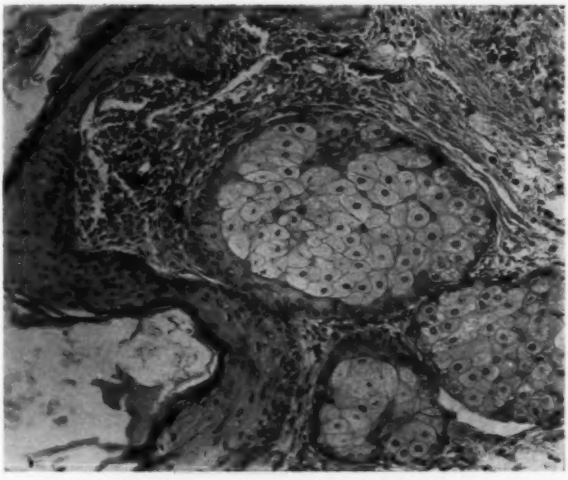

FIGURE 2: Microscopic section of 1.

Wakeley[3] found only 0.24 per cent of all substernal goiters to be totally intrathoracic.

In 1953, Maier[5] stated that substernal thyroids were the most common abnormal occupant of the superior mediastinum. Of our entire series 13 per cent were in this category. These thyroid growths are often found on routine chest x-ray films. (20 per cent in our series). When patients do complain, the nature of the complaints is usually due to obstructive symptoms such as dyspnea, dysphagia or hoarseness.

Fluroscopic examination will show movement of the mass with deglutition. The Valsalva maneuver may also be used successfully to delineate the mass.

Microscopically there were eight benign adenomas and three cases of thyroid carcinoma.

Radioactive iodine is of help in establishing a diagnosis. If functioning gland is present behind or below the sternum the test will be positive in over 95 per cent of cases.

Thymomas

The majority of thymomas are malignant. Three of our five cases were so diagnosed. Thymomas are usually seen in the anterior or superior mediastinum. The benign thymic tumors are more often associated with myasthenia gravis than are the malignant variety. A superior mediastinal mass situated somewhat anteriorly should raise a high index of suspicion. The mass cannot, however, be distinguished from mediastinal lymphoid tissue.

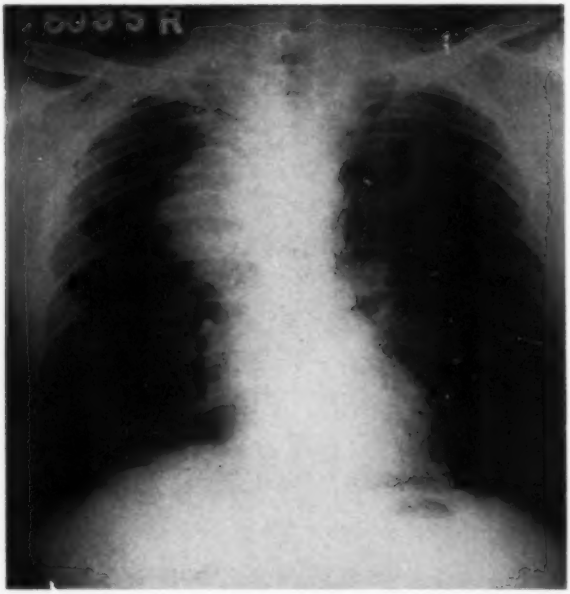

FIGURE 3: Intrathoracic thyroid CA, 52 year old man with two year history of vague chest complaints. Note lower border of lesion is at level of fourth rib anteriorly.

Tumors of Mesenchymal Origin

This group includes tumors of connective tissue, adipose tissue, cartilage, smooth muscle, blood and lymphatic vessels. Not infrequently two or more of these tissues are prominent in a single neoplasm. All of these tumors are uncommon to rare. At least 20 different types have been described. This group comprised 23 per cent of our series.

Ten of the cases were leiomyomas of the esophagus. These patients were treated and operated on the service of Drs. Charles B. Puestow and William J. Gillesby.[10] To 1950, Daniel[11] had only collected 92 cases from the literature.

Mesothelioma is a generic term for a group of neoplasms which take origin from the pleura. Localized fibrous mesotheliomas and the diffuse malignant type differ in gross and microscopic features as well as in their clinical appearance, course, therapy and prognosis. Localized fibrous mesothelioma has recently been re-evaluated by Clagett.[12] This lesion is unique because the symptoms are almost all extrathoracic! Patients complain of attacks of chills and fever, swollen and migratory involvement of joints of the extremities and clubbing of the fingers and toes. Prompt regression of these symptoms usually occurs following removal of the tumor. Our series show two cases of diffuse malignant mesothelioma which apparently arose from the mediastinum.

Teratomas

Willis[13] has stated that the average age for mediastinal teratomas is 27 years. The average age of our 11 patients was 41. These tumors are usually not symptomatic until they attain considerable size. Malignant teratomas are more commonly seen in men.

In 90 per cent of our cases, the lesion was situated in the anterior mediastinum. Except for lymphomas, teratomas are the most common lesion in the anterior mediastinum. In five large series, the percentage

FIGURE 4: Hemi-section of lesion in Figure 3.

of malignant change varied from 11 per cent to 44 per cent. Our percentage was 18 per cent. Two of our cases were benign cystic teratomas (dermoid cysts). Of the remaining nine, two were malignant.

Many of these patients are asymptomatic, the lesion being found on routine chest x-ray film. Symptoms, if at all present, include vague pain in the chest, cough and dyspnea. As the tumor increases in size the patient may complain of pressure symptoms. The malignant teratomas finally infiltrate the adjacent structures and the patient shows the symptoms of superior vena caval obstruction. Occasionally a cyst can rupture into a bronchus producing expectoration of sebaceous matter with hair and pus. Unless teeth or bone are visible on x-ray film, the diagnosis cannot be established. Lateral x-ray film showing an anteriorly placed mass is a suggestive finding. If left undisturbed, these tumors almost always contribute to the death of tthe patient; this was true in 95 per cent of Rusby's[14] series.

Heuer[15] found that 47 of 48 patients with untreated teratomas died from their tumors. The treatment is early excision — *before* the onset of malignant change.

Miscellaneous Lesions

Such a grouping of clinical material would not be complete without those lesions which caused a problem in the differential diagnosis of mediastinal space-occupying lesions.

Had angiocardiography been in vogue a few years earlier three of the four patients with aneurysms in the mediastinal area would have been spared a needless thoracotomy. Six cases of bronchogenic carcinoma were misinterpreted as being in the mediastinum. Current practices in our routine pre-surgical workup might have given us a better insight into these cases. Scalene node biopsy should be used routinely. Despite these newer aids, the majority of mediastinal tumors have resisted our present methods of diagnosis — except for thoracotomy.

Conclusions

One hundred seventeen patients with mediastinal masses are presented. These were seen over a 25 year period at the Veterans Administration Hospital, Hines, Illinois.

Since our group was composed of 99 per cent adult men, our group percentages differ from others presented in the literature. No other large series ever reported less than 8 per cent of neurogenic tumors — ours was 4 per cent. The usual percentage of mesenchymal tumors is around 10 per cent, ours was 23 per cent. Only when all large thoracic surgical centers report their series will we have a true insight into the frequency of various types of mediastinal tumors.

In describing 112 cases of mediastinal tumors, we have shown again that the percentages of these lesions vary considerably from series to series.

Lesion	Expected Percentage	Our Percentage
Neurogenic tumors	30 per cent	4 per cent
Teratomas	20 per cent	10 per cent
Thymomas	10.5 per cent	4 per cent
Bronchogenic cysts	10 per cent	14 per cent
Intrathoracic thyroids	7 per cent	13 per cent
Pericardial cysts	6 per cent	3.5 per cent

Careful interpretation of good x-ray films is still the most valuable tool in making a preoperative diagnosis of a mediastinal neoplasm. Certain special radiographic procedures such as laminograms and angiocardiograms can help us make a more intelligent guess at the diagnosis. Scalene node biopsy has become a useful tool. We agree with Sabiston[16] that delay for extensive diagnostic workup is usually not indicated.

In Nelson's[4] series there was a zero mortality in 97 thoracotomies for these lesions. Early surgery is diagnostic and can be, in many instances, curative for a mediastinal mass.

SUMMARY

One hundred seventeen mediastinal masses in adults have been described. There were 38 different histologic types seen. It is evident that a specific preoperative diagnosis will be unlikely. Therefore we believe that early thoracotomy is advisable. We have also shown that there can be wide variance from "expected percentages" of these lesions.

RESUMEN

Se han descrito ciento diecisiete masas mediastinales en adultos. Se observaron 38 diferentes tipos histológicos. Es evidente que un diagnóstico específico preoperatorio será improbable.

Por tanto creemos que la toracotomía inmediata es de aconsejarse. También hemos demostrado que puede haber gran variación de los "porcentajes esperados" en estas lesiones.

RESUMÉ

L'auteur a décrit 117 cas de masses médiastinales chez des adultes. Il y eut 38 modalités histologiques différentes. Il est évident qu'un diagnostic spécifique préopératoire serait très difficile. C'est pourquoi l'auteur pense qu'une thoracotomie précoce est souhaitable. Il a montré également qu'il pouvait y avoir une grande variabilité du "pourcentage attendu" de ces lésions.

ZUSAMMENFASSUNG

117 Mediastinaltumoren bei Erwachsenen wurden beschrieben. Es fanden sich dabei 38 voneinander abweichende histologische Typen. Es liegt auf der Hand, daß eine spezielle präoperative Diagnose unwahrscheinlich sein wird. Wir sind deshalb der Ansicht, daß eine frühzeitige Thorakotomie ratsam ist. Wir konnten ferner zeigen, daß bei diesen Veränderungen weite Schwankungen vorkommen können hinsichtlich der "erwarteten Prozentsätze."

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Physiological Research in Chronic Pulmonary Disease: An Evaluation of Alveolar Aeration, Oxygen and Carbon Dioxide Transfer and the Pulmonary Circulation*,**

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Introduction

This discussion of physiological research in chest medicine will be related primarily to the clinical evaluation of the ability of the lungs to supply oxygen to and remove carbon dioxide from the blood adequately during rest and exercise. The physiologic disturbances may be grouped under three major aspects; impairment in alveolar aeration on the ventilatory side, hypoxia and hypercapnia from disturbances in the transfer of oxygen and carbon dioxide in the lung and abnormal pulmonary circulation, manifest especially during exercise because of the lack of expansibility of the pulmonary vascular bed.

Alveolar Aeration

Measurements pertaining to alveolar aeration include spirograms,[1-6] (total, timed, mid-expiratory and maximal breathing capacity), residual air, intrapulmonary mixing, evaluation of bronchospasm and special devices for air flow. Air flow can be evaluated from spirogram recordings on various types of mechanical spirometers, electronic recordings using pressure sensitive transducers and more recently developed apparatus for measuring instantaneous maximal peak flow. The instantaneous peak flow measurement has been recently simplified by the development of two devices, one in the United States (commonly known as the Puff Meter)[7] and in England, the Wright peak flow meter.[8] These devices measure the instantaneous flow after taking in as deep a breath as possible and then blowing out as rapidly as possible. The stop device on the Wright peak flow meter holds the needle at the highest instantaneous flow attained on the rapid exhalation, a feature which makes the reading of the measurement very easy and accurate. The stop device is an improvement over the Puff meter where the rapid highest deflection of the needle has to be observed directly.

The volume and speed of exhalation on the spirogram may be measured from the 0.5 sec., 1.0 sec., or 3.0 sec., timed vital capacity. The three seconds timed vital capacity should be expressed in relation to the predicted total vital capacity (normal 100 per cent), rather than the observed vital capacity for the greatest reliability, Figure 1. The various air flow methods measure the rapidity with which air can be exhaled from the lungs. The three second timed vital capacity as per cent of the

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predicted normal total vital capacity was correlated with the maximal peak flow as obtained on the Wright flow meter, Figure 2a. The maximal breathing capacity as per cent of normal predicted was correlated in a similar manner as for the three second timed vital capacity, Figure 2b. The correlation was better for maximal breathing capacity than for the three second timed vital capacity. The spread was quite large for individual cases for maximal flows above 200 liters per minute for the timed vital capacity and 350 liters per minute for maximal breathing capacity, Figure 2. The usefulness of this measurement needs further evaluation.

Significant information on air trapping is provided from the shape of the recorded spirogram tracing. The maximal breathing capacity provides significant information on the bellows action of the chest and lungs in addition to the timed vital capacity measurements or other types of instantaneous flow measuring devices. Bronchospasm in our experience is best evaluated from measurements of the maximal breathing capacity before and after the administration of a bronchodilator drug. Consistent check measurements are more difficult to obtain in some individuals on peak flow devices than on spirograms. Since the spirogram is a graphic recording, the operator can observe and instruct the subject better to insure obtaining maximal values.

The residual air measurement and tests of intrapulmonary mixing are very important in the evaluation of lung function. The helium closed circuit method for residual air has greatly simplified this test from the standpoint of accuracy, speed and cost for the patient. The

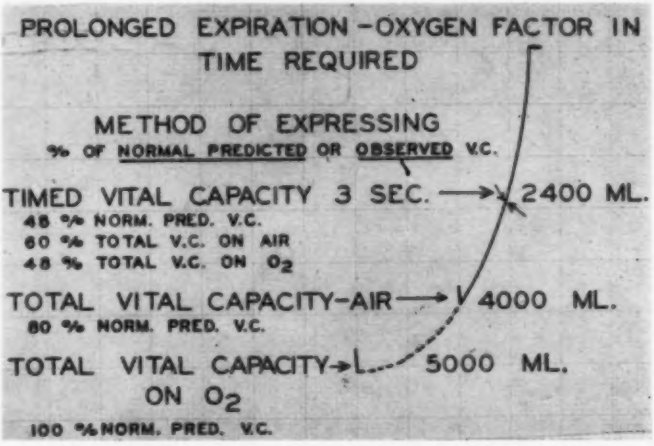

FIGURE 1: With prolonged exhalation the maximal volume varies with air and oxygen breathing in some cases as shown above. The breath can be held longer on oxygen breathing as compared to air breathing. In the above case oxygen breathing permitted the subject to blow out longer as compared to the air breathing, but the functional significant part, the three second timed vital capacity, was not increased on the oxygen breathing. The timed vital capacity expressed as per cent of observed was misleading on air breathing in the above case, and similar differences may occur after bronchodilator or other treatment procedures. Expressing the timed vital capacity for three seconds as per cent of the normal predicted vital capacity appears more accurate, and the releationship is independent of air or oxygen breathing or after bronchodilator or other treatment procedures.

helium closed circuit method appears to be the method of the future. In our experience for the past four years with an improved modification and procedure,[9] the helium method is more accurate than the oxygen open circuit for measuring residual air in severe emphysema unless a nitrogen meter is used for monitoring the nitrogen washout, and with this procedure the two methods check closely. The residual air has been found a most sensitive test to reflect changes in the pulmonary status; for example, an increase in the residual air detects early change from breathing Los Angeles smoggy air sooner than the timed vital or maximal breathing capacity tests.[10] The range of the residual measurement may vary from 40 per cent to 400 per cent of the normal predicted value,

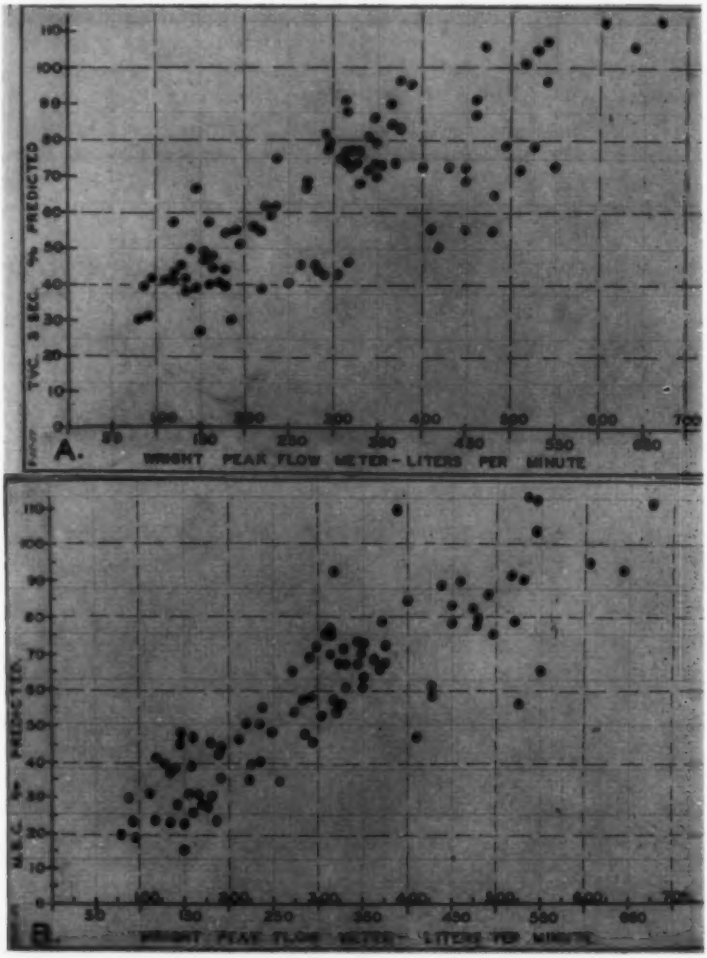

FIGURE 2: Correlation of the instantaneous peak flow as obtained on the Wright Peak Flow Meter as liters per minute with (a) the timed vital capacity for three seconds as per cent of the normal predicted, and (b) the maximal breathing capacity as per cent of the normal predicted.

a wider spread than any other tests currently used in lung function. The residual air measurement may be poorly correlated with the chest roentgenogram, especially in pneumoconiosis.

The functional residual capacity may be misleading in the individual case. Shifts in the level of the diaphragm results in wide variations, Figure 3. Apprehension and tenseness with significant shifts in the level of the diaphragm are observed frequently. The expiratory reserve should be determined at the beginning of each residual air measurement, just before the subjects air breathing circuit is turned to connect to the helium closed or oxygen open circuit. The residual air measurement should be used in the overall evaluation of emphysema rather than the functional residual capacity.

The nitrogen washout on oxygen breathing employing a nitrogen meter with continuous recording of each breath in a most sensitive test for the evaluation of intrapulmonary mixing in the lungs.[11,12] This test is very reproducable and reveals most graphically the presence of extensive obstruction in many of the smallest respiratory air passageways in asthma and emphysema. The nitrogen washout curve was obtained with oxygen breathing until an end tidal of 1 per cent was reached, a method not significantly different from measuring the amount of nitrogen washed out per breath.[12] The nitrogen washout was correlated with the residual per cent of total lung capacity (TLC) in 235 cases with values ranging from normal to most severe emphysema.[13] In the group of cases with a residual from 20-25 per cent of TLC, the composite graph of the nitrogen washout revealed an end tidal of one per cent in four minutes, Figure 4. These data were tabulated for the other cases by groups based on the residual per cent of TLC., Table 1. There was no significant difference in the composite nitrogen washout for groups with residual per cent of TLC from 35-40, 40-45, and 45-50, and the average time was eight minutes to obtain an end tidal of 1 per cent (moderately prolonged). In the group with a residual from 50-60 per cent of TLC, the nitrogen washout time was significantly increased, average 13.5 minutes, (markedly prolonged), to an end tidal of 1 per cent, and the

TABLE 1 — NITROGEN WASHOUT STUDIES WITH THE NITROGEN METER*

Group	No. of Cases	Residual per cent of Total Lung Capacity	Average Time on Oxygen to End Tidal of 1 per cent, Minutes	Average Alveolar N_2 at End of Oxygen Breathing, per cent
1	19	20-25	4.0	1.42
2	29	25-30	5.5	1.62
3	38	30-35	6.0	1.85
4	26	35-40	8.0	2.12
5	34	40-45	8.0	2.12
6	21	45-50	8.0	2.25
7	36	50-60	13.5	2.80
8	24	60-70	15.5	3.60
9	9	70 & +	17.0	3.54

*See Figure 4.

In most of the cases the emphysema was of a moderate degree in groups 4, 5 and 6, of a severe to very severe degree in groups 7, 8 and 9, and of an insignificant degree in the first three groups.

group from 60-70 was still more prolonged, 15.5 minutes. In eight cases with residual above 70 per cent of TLC, the nitrogen washout was markedly prolonged, average 17 minutes. The pulmonary nitrogen was not washed out even after 15-20 minutes on oxygen breathing in some severe emphysema cases. In these cases the helium closed circuit residual air measurement was usually higher than on the oxygen open circuit for the usual seven minutes[14] washout, but the residual volumes by the two methods check when the oxygen washout time was extended to 10-15 minutes. Seven minutes is an inadequate time to wash out the pulmonary nitrogen on oxygen breathing in determining residual air in many emphysema cases.

The curve of nitrogen exhalation with the single deep breath of oxygen[15] and the nitrogen meter has not been found satisfactory to evaluate intrapulmonary mixing on a quantitative basis. The nitrogen single deep breath test has been observed to improve after breathing an irritant such as cigarette smoke, and to worsen after a bronchodilator treatment with Isuprel,[16] just the reverse of the vital capacity measurements obtained at the same time. This would indicate that the single deep breath test reflects primarily the better ventilated alveoli, and after a bronchodilator[17] treatment some poorly ventilated alveoli are opened enough to participate so that the nitrogen curve reflects the increased number of alveoli ventilated.

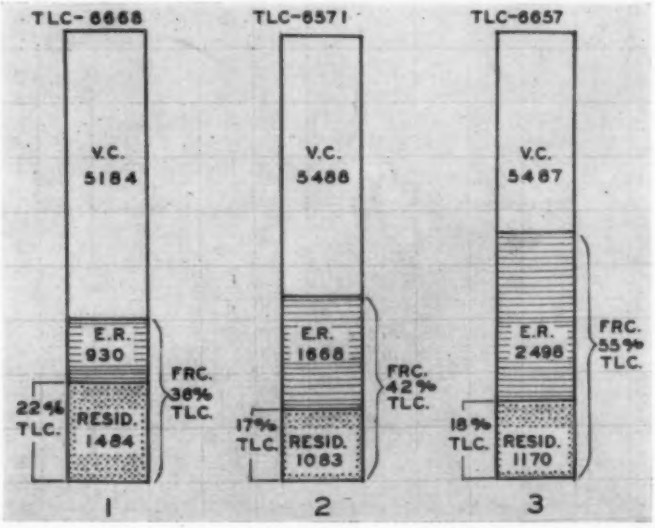

FIGURE 3: The lung volume measurements are shown for three normal subjects. The residual air measurement was normal with respect to the predicted. The expiratory reserve (ER) varied from 930 to 2498 ml. in the three subjects, with corresponding changes in the functional residual capacity (FRC), sum of residual plus expiratory reserve. The functional residual capacity ratio to total lung capacity (TLC) was 36 per cent in the first case, 42 per cent in the second and 55 per cent in the third, while the ratio of the residual air to the total lung capacity was normal in all three cases. The total lung capacity was normal and about the same in the three cases. The functional residual capacity would be misleading for evaluation in number three above as compared to number one.

Valuable information has been provided from many research studies on the pressure volume relationship of the lung (compliance studies).[18] These studies have helped explain particularly the increased work of breathing in fibrosis and emphysema. The overall evaluation of compliance has been best correlated clinically with total vital capacity. The necessity of passing a balloon in the upper esophagus is a disadvantage for the routine use of this test. For satisfactory clinical evaluation the compliance test does not appear to provide any more significant information than obtained from the spirogram. The body plethysmograph[19] is an interesting device for studying factors relating to air flow and other aspects of breathing, but its clinical application awaits further extensive research evaluation.

Oxygen and Carbon Dioxide Transfer

The adequacy of the oxygen and carbon dioxide transfer in the lung is evaluated primarily from the arterial blood oxygen saturation and carbon dioxide content at rest and with exercise. Arterial hypoxemia occurs in the presence of poorly ventilated alveoli and from the perfusion of blood through non-ventilated areas of the lungs. Such non-ventilated areas amount to small shunts from right to left, and are present in fibrosis, atelectasis, the collagen group of diseases and other restrictive conditions of the lungs. Cyanosis may also occur from right to left shunts either in the heart (congenital heart disease) or in the lungs, (arterial venous fistula). In chronic pulmonary disease the significant decrease in the arterial blood oxygen saturation is due primarily to the presence of poorly ventilated alveoli perfused with blood and to the perfusion of blood through non-ventilated areas, where air flow is blocked above

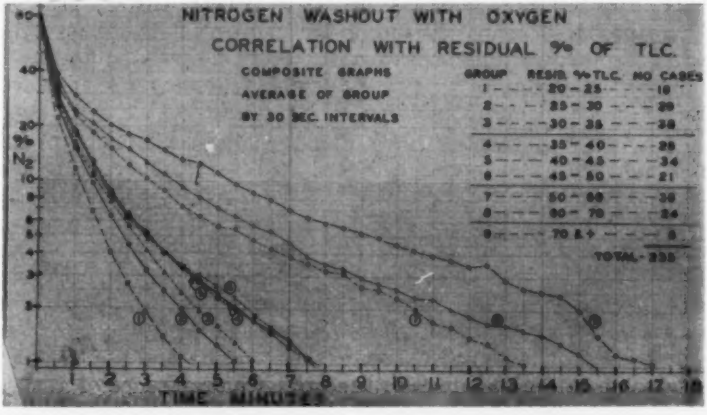

FIGURE 4: Nitrogen washout curves obtained with a nitrogen meter on oxygen breathing with continuous recordings of each breath in 235 cases. The peak per cent of nitrogen in the expired air was plotted on the ordinate on semilogarithmic paper and correlated with time at 30 seconds intervals on the abscissae. The nine groups were separated on a basis of the residual air as per cent of total lung capacity. The residual air was measured both by the oxygen open circuit and the helium closed circuit methods. The nitrogen washout curve for group one represents the composite of 19 cases at each 30 second interval of the nitrogen washout to an end tidal of 1 per cent. The curves for the other groups were plotted in a similar manner, also see Table 1.

the alveolar level at which gas exchange can occur. This latter situation actually constitutes a small shunt at the alveolar level. The increased cardiac output of exercise as compared to rest opens up more capillaries in areas where the ventilation perfusion abnormalities are most extensive. A 32 to 40 per cent oxygen breathing gas will not obscure the small shunts at the alveolar level especially with exercise, but breathing 100 per cent oxygen does obscure them, especially at rest, because of the very marked increase in oxygen dissolved in the plasma.[20] The use of 100 per cent oxygen breathing can be used to rule out large shunts from right to left, but not the small ones. The 32 per cent oxygen breathing gas increases the inspired pO_2 to above 70 mm. Hg. and is more than adequate to overcome an alveolar-capillary membrane block if this be a significant factor in the production of hypoxia. Intermittent positive pressure breathing improves the ventilation of the poorly ventilated alveoli, so that the oxygen partial pressure becomes more nearly normal in the alveoli even on compressed air breathing, and the blood perfusing these alveoli approaches the normal saturation.[21] The physiological studies show that the improved saturation results from the more uniform alveolar aeration. In interstitial pulmonary fibrosis even in the absence of emphysema, the primary defect producing the hypoxia is the perfusion of blood through non-ventilated or very poorly ventilated areas, rather than an alveolar-capillary membrane block.[20] In my experience the existence of an alveolar-capillary membrane block as the primary significant factor for hypoxia is very rare. We have not studied acute beryllosis or hyaline membrane disease, conditions in which studies are needed using graded levels of high oxygen breathing. A low diffusing capacity measurement (carbon monoxide steady state or other methods) is not necessarily related to an alveolar-capillary membrane block, but rather to a number of other factors, the decreased surface area for gas exchange probably being the major factor in most instances. In some situations studied in this laboratory the pulmonary blood flow and ventilation have been found significant factors affecting the carbon monoxide diffusing capacity measurement. The diffusing capacity measurements for carbon monoxide are markedly decreased in many cases of severe emphysema and fibrosis, where there is no evidence of an alveolar-capillary membrane block, but the alveolar surface area for gas exchange is markedly decreased.

Hypercapnia when present in emphysema is a significant measurement, but a normal or decreased CO_2 content does not indicate the absence of emphysema. Hypercapnia indicates the need for treatment to increase alveolar ventilation, such as mechanical respiratory assistance or even tracheotomy in some cases.[22-24] The arterial blood pH is most valuable in the diagnosis of the presence or absence of respiratory acidosis.[25] The arterial pH when properly performed anaerobically on a glass electrode is diagnostic and may be life saving. Fortunately the pH determination is a simple test and the apparatus is compact, portable and relatively inexpensive.* Hospitals with a clinical laboratory should be able to perform the pH measurement, so that a doctor can order arterial pH on all undiagnosed patients in a stuperous or comatose

*Cambridge, Research Model, very satisfactory.

condition. Many deaths have occurred from unrecognized respiratory acidosis.[23] The calculated pH is inaccurate in many cases, especially emphysema. The CO_2 combining powers on venous blood may be misleading in respiratory acidosis and is completely unreliable. The calculated pCO_2 from the Van Slyke arterial CO_2 content, oxygen content and saturation and pH on the glass electrode in most cases of emphysema was low as compared to the direct tension measurement of the pCO_2 on the same blood sample, Figure 5. Measurements of the alveolar pCO_2 from a forced exhalation on a CO_2 analyzer were usually too low also in emphysema. The use of a high CO_2 breathing mixture (8 per cent CO_2) for equilibration on the rapid infra-red CO_2 analyzer, as reported by Hackney et al,[26] has not proved an accurate method in our experience for arterial pCO_2 in severe emphysema. The change in CO_2 content of arterial blood is slower than changes in pCO_2 as correlated with alveolar aeration.

Pulmonary Circulation

There is great need at the present time for further studies on the pulmonary circulation in chronic pulmonary disease. Inability to expand the pulmonary vascular bed in a normal manner is a very common occurrence.[27] Better drugs are needed to treat the increased pulmonary vascular resistance and to supplement aminophylline, which is probably the best single drug available at the present time.[28] The early diagnosis and treatment of increased pulmonary vascular resistance

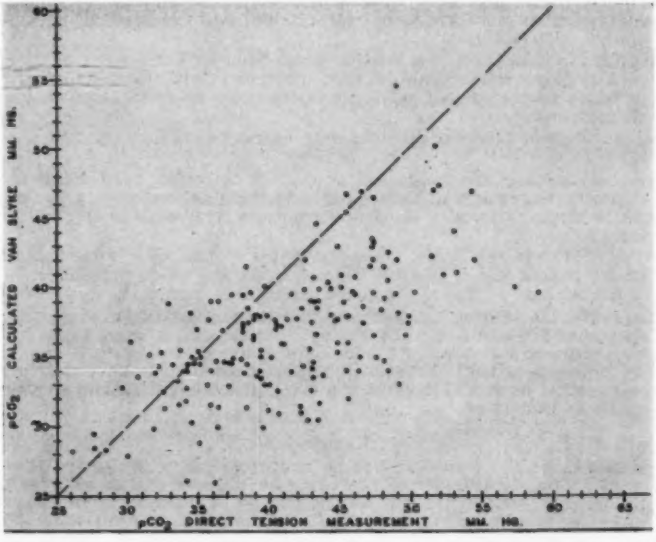

FIGURE 5: The arterial pCO_2 by the direct tension bubble measurement of Riley was correlated with the calculated pCO_2 from Van Slyke measurements of CO_2 content and oxygen saturation and the pH on a glass electrode. The direct tension measurement of pCO_2 was usually higher than the calculated values which tended to be too low in emphysema. Hyperventilation may occur when an individual has a nose clip on and breathes through a rubber mouth piece, and ventilation changes will be reflected immediately in the arterial pCO_2 (direct tension measurement) and the pH, but a time lag occurs for the CO_2 content to change.

is essential. The oxygen uptake for the one minute step-up test has been very helpful in detecting changes in the pulmonary circulation without the necessity for cardiac catheterization.[27] If the external ventilation is adequate and the exercise oxygen uptake on air breathing markedly decreased, there is indication of the inability to increase the pulmonary blood flow in an amount corresponding to the degree of exercise given and indirectly an indication of the presence of increased pulmonary vascular resistance.

SUMMARY

An adequate clinical evaluation of pulmonary function requires measurements on the ventilatory status, on the transfer of oxygen and carbon dioxide in the lungs and on the pulmonary blood flow. Single tests of lung function on only one aspect are unsatisfactory. There is need for more extensive application of accurate pulmonary function testing, for better diagnosis of the individual case for medical treatment, for better surgical evaluation in the problem case and more accurate disability appraisal in compensation cases. The pulmonary function evaluation should be used along with the history, the physical and the roentgenological examination. Spirograms are satisfactory screening tests, but lung volume measurements are required for accurate evaluation of emphysema and fibrosis. Measurements on arterial blood and the expired air complete the pulmonary function evaluation. The clinician, chest surgeon, consultant or others, when provided with an accurate pulmonary function evaluation of their problem cases, will come to use and rely on this new field of medicine more and more. On the other hand, inadequate pulmonary function testing will have the reverse effect engendering suspicion and distrust. The pulmonary physiologist must employ an adequate battery of tests well standardized and suitable for routine use on the individual case regardless of the problem, and the information obtained must be interpreted correctly and be dependable for use in arriving at a decision for the best method for handling or managing the individual problem case.

RESUMEN

La valuación adecuada de la función pulmonar requiere la medida de la condición ventilatoria, de el recambio de oxígeno y anhidrido carbónico en los pulmones, y del flujo sanguínco pulmonar. Las pruebas aisladas de la función pulmonar sobre sólo un aspecto, no son satisfactorias.

Se necesita una aplicación mas amplia de las pruebas funcionales pulmonares mas exactas para el mejor diagnóstico del caso individual para tratamiento médico, para mejor valuación, para cirugía y para una estimación mas exacta de la incapacidad en casos de compensación.

LaL valuación de la función pulmonar debe usarse con la historia clínica, el examen físico y el radiológico.

Las pruebas por los espirogramas son pruebas de detección, pero se necesitan medidas del volumen pulmonar para la exacta estimación del enfisema y la fibrosis. Las medidas en la sangre arterial y en el aire expirado completan la valuación completa de la función pulmonar.

El clínico, el cirujano de tórax, los consultantes u otros, cuando se les proporciona una valuación exacta de la función pulmonar de sus casos-problemas, llegarán a usarlos y a confiar mas y mas en este nuevo campo de la medicina.

Por otra parte, las pruebas pulmonares inadecuadas tendrán el efecto contrario al suscitar sospechas y desconfianza. El fisiólogo pulmonar debe emplear un conjunto de pruebas bien estandarizados y apropiados para el uso de rutina en el caso individual en cualqier problema y la información obtenida debe interpretarse correctamente y debe poderse confiar en ella al llegar a una decisión sobre el método mejor para tratar un caso-problema individual.

RESUMÉ

Une évaluation clinique convenable de la fonction pulmonaire demande des mesures de l'état ventilatoire, du transfert d'oxygène et de gaz carbonique dans las poumons, et du débit sanguin pulmonaire. Un test unique de la fonction pulmonaire basé sur un seul aspect n'est pas satisfaisant. Il est nécessaire d'avoir une application plus extensive du test précis de la fonction pulmonaire pour un meilleur diagnostic du cas individuel pour le traitement médical, pour une meilleure évaluation chirurgicale dans les cas qui posent un problème, et une estimation plus précise de l'infirmité dans les cas qui sont sujets à pension. L'évaluation de la fonction pulmonaire devrait être utilisée autant que les antécédents, l'examen clinique et radiologique. Les spirogrammes sont des tests satisfaisants, mais les mesures du volume pulmonaire sont nécessaires pour une évaluation précise de l'emphysème et de la fibrose. Des mesures portant sur le sang artériel et l'air expiré complètent l'évaluation de la fonction pulmonaire. Le clinicien, le chirurgien thoracique, le consultant, etc . . . quand ils sont en possession

d'une évaluation précise de la fonction pulmonaire de leurs cas, utiliseront de plus en plus ces méthoodes et s'appuieront sur ce nouveau champ de la médecine. D'un autre côté, un test de la fonction pulmonaire mal fait aura un effet contraire en endendrant la suspiscion et le doute. Le physiologiste pulmonaire doit utiliser un ensemble convenable de tests bien standardisés et applicables à l'usage courant sur les individus, sans lien avec le problème et l'information obtenue doit être interprétée correctement et doit être utilisée pour arriver à la décision par la meilleure méthode de conduite devant chaque cas particulier.

ZUSAMMENFASSUNG

Eine ausreichende klinische Ermittlung der Lungenfunktion erfordert Messungen der Ventilationsverhältnisse, des Austausches von Sauerstoff und Kohlensäuren in der Lunge und dir pulmonalen Strömungsgeschwindigkeit des Blutes. Einzelwerte der Lungenfunktion unter nur einem Gesichtspunkt sind unbefriedigt. Es ist erforderlich, sorgfältigste Lungenfunktionsprüfungen in größerem Umfang vorzunehmen. Damit der Einzelfall für die internistische Behandlung besser zu beurteilen ist, und der Grenzfall in chirurgischer Hinsicht besser zu bewerten ist und damit schliesslich die Fälle von Entschädigungsansprüchen eine genauere Auswartung ihrer Leistungsminderung erfahren, muß man die Beurteilung der Lungenfunktion gemeinsam mit der Anamnese, der körperlichen und der röntgenologischen Untersuchung, vornehmen. Spirogramme sind befriedigende Suchverfahren, jedoch sind Bestimmungen der Lungenvolumina erforderlich zur genauen Feststellung von Emphysem und Fibrose. Messungen am arteriellen Blut und der Ausatmungsluft vervollständigen die Ermittlung der Lungenfunktion. Der klinisch tätige Arzt, der Thoraxchirurg, der Konsiliarius und andere werden, wenn sie über eine exakte Ermittlung der Lungenfunktion für ihre Grenzfälle verfügen, mehr und mehr von diesem neuen Gebiet der Mdizin Gebrauch machen und sich darauf verlassen. Auf der anderen Seite werden mangelhafte Lungenfunktionsproben, die umgekehrte Wirkung haben und Verdacht und Miβtrauen hervorrufen. Der Lungen-Physiologe muß eine entsprechende Vielzahl von Testen einsetzen, die gut standardiziert und für den routinemässigen Gebrauch jedes einzelnen Falles geeignet sind, unbeschadet der jeweiligen Fragestellung. Die gewonnenen Werte müssen korrekt interpretiert werden, zuverlässig in der Anwendung sein, um zu einer Eentscheidung zu kommen über die beste Methode der Handhabung oder Führung des individuellen fraglichen Falles.

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A New Method of Controlling Paradoxical Respiration in Single Stage Thoracoplasty

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Introduction

It is felt by the authors that there is still a distinct place for thoracoplasty in the treatment of pulmonary tuberculosis. We believe that attempts to treat every surgical case by resection will result in complications and deaths which could have been avoided by the occasional use of thoracoplasty. Furthermore, if a classical thoracoplasty could be done as described by Alexander,[1] in a single stage, it would be less of a second choice than it is at present. It is not our aim to change the method of obtaining collapse. We have only added a simple maneuver which controls paradoxical respiration and permits three stages to be done in a single operation.

The major difficulty in accomplishing thoracoplasty in a single stage is the control of paradoxical motion of the chest wall after the removal of the ribs. The problem of blood loss, which previously supported the dictum of multiple stages, has been swept aside by the availability of adequate amounts of blood. We are not satisfied with plombage procedures or lesser degrees of the classical thoracoplasty to obtain a single stage thoracoplasty.[2-7] For these reasons we have developed the following technique.

Method

A single stage thoracoplasty is accomplished, using a posterolateral thoracoplasty-type incision with removal of the third, second and first ribs entirely, including transverse processes. At this point, paradox becomes apparent and can be controlled by suturing as indicated in Figure 1. The suture material employed is #1 or #2 chromic catgut and an anchoring "bite" is taken of the sacrospinalis muscle. Subsequent superficial "bites" with the needle are taken of the intercostal muscles until the sternal origins of the pectoralis major are reached. Here a final anchoring "bite" is taken and the suture is tied. The fourth, fifth and sixth ribs, including transverse processes, are then taken in the customary fashion and one or two more sutures are taken as before. If the operator wishes, he may take out the seventh, eight and ninth ribs, including transverse processes, followed by one or two more sutures to obtain control of the paradoxical motion encountered following their removal. Repiacement of blood loss, as indicated by sponge weighing techniques, is carried out simultaneously. The line of sutures may be employed in a direction parallel with the rib bed; however, it is easier and more effective to place them across the rib beds in a horizontal direction, as indicated in Figure 1. Control of paradoxical motion is sometimes more effectively controlled by tying all the ligatures after the desired number of ribs have been removed.

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Data

Our series is divided in two groups. The first group (23 cases) received a classical thoracoplasty of five to eight ribs with control of paradoxical respiration by the method outlined above. The indication for surgery was pulmonary tuberculosis with cavitary lesions which had failed to respond to anti-tuberculous drugs. All of the patients were poor risks and were not considered acceptable for resectional surgery. In this group, 16 of the 23 patients had far advanced disease and 15 had bilateral disease evident at the time of operation. Seven of the patients had had interrupted courses of chemotherapy prior to surgery. One patient expired on the sixth postoperative day from a massive pulmonary hemoptysis. Autopsy was denied. One had a reactivation one month postoperatively and later required a resection for removal of his lesion.

Of the remaining patients, no complication was encountered. Our longest follow-up is four years. The sputum or gastric washings are negative in all but one (21 cases). In these cases we do not believe we could have done as well if we had employed resections.

The second group consisted of an additional 12 patients with nontuberculous disease who required thoracoplasty for varying reasons. From four to 11 ribs were removed in one stage in these cases without complications or evidence of paradoxical respiration.

Discussion

We have found that we can obtain a more efficient collapse by single stage thoracoplasty than when multiple stages are employed. The single stage procedure has been well tolerated. We fully expected that resection in many of these cases would be necessary, but to date only one has been necessary for thoracoplasty failure.

Our experience in controlling paradox by the above method has been satisfactory. We are not advocating return to thoracoplasty as the prime treatment for cavitary

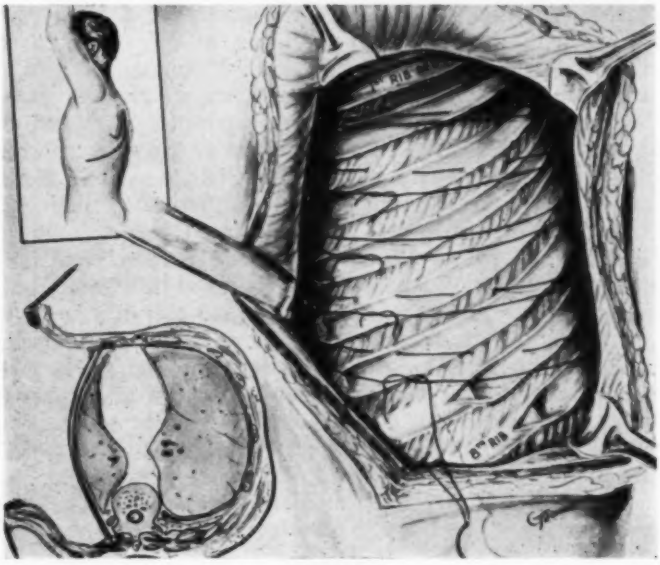

FIGURE 1

tuberculosis, but we feel that a surgeon who will not do an occasional thoracoplasty will be forced to deprive a few patients of the benefits of surgery.

The surgical maneuver to control paradoxical respiration consists of properly placed sutures and is quickly and easily done.

SUMMARY

There is still a distinct place for the use of thoracoplasty in the treatment of tuberculosis and the occasional use of thoracoplasty in the poor risk type of patient can be very effective when supplemented by adequate anti-tuberculosis drugs. The method described is that of a classical thoracoplasty initiated by Alexander, and done in a single stage. Control of paradoxical respiration is easily accomplished by placing anchoring sutures from the sacrospinalis muscle to the pectoralis major, as indicated in Figure. From four to 11 ribs have been removed, including the transverse processes in 35 patients, with one death. The results of the surgery have been gratifying.

RESUMEN

Hay aún un lugar definido para el uso de la toracoplastía en el tratamiento de la tuberculosis y el uso ocasional en el enfermo que constituye un mal riesgo puede ser muy efectivo cuando se proporcionan las drogas antituberculosas convenientes. El método descrito es el de la toracoplastía clásica iniciada por Alexander y realizada en un solo tiempo. El control de la respiración paradójica es fácil de realizarse colocando suturas de fijación desde el sacroespinal hasta el pectoral mayor según se indica en la Figura 1. Se han resecado de 4 a 11 costillas incluyendo las apófisis transversas en 35 personas con una defunción.

Los resultados de la cirugía han sido satisfactorios.

RESUMÉ

Il existe encore une place précise pour l'utilisation de la thoracoplastie dans le traitement de la tuberculose et son emploi éventuel chez les malades à qui on ne peut faire courir que de petits risques, peut être efficace lorsqu'elle est complété par la prescription des médications antituberculeuses convenables. La méthode décrite est la thoracoplastie classique d'Alexander, pratiquée en un seul temps. Il est facile d'empêcher la respiration paradoxale en suturant le muscle spinal au grand pectoral, comme indiqué dans la Figure 1. De quatre à onze côtes ont été enlevées, avec les transverses chez 35 malades. Il y eut un seul décès. Les résultats de l'opération sont encourageants.

ZUSAMMENFASSUNG

Es gibt immer noch einen bestimmten Platz für den Einsatz der Thorakoplastik bei der Behandlung der Tuberkulose. Die gelegentliche Anwendung der Thorakoplastik bei Patienten, deren Operation ein schlechtes Risiko bedeutet, kann sehr wirksam sein, wenn sie durch eine entsprechende antituberkulöse, medikamentöse Therapie unterstützt wird. Die beschriebene Methode besteht in einer klassischen Thorakoplastik, wie sie durch Alexander zuerst angegeben und in einer einzigen Sotzung durchgeführt wird. Die Kontrolle der paradoxen Atmung läβt sich leicht durchführen durch Herstellung von Haltefäden zwischen dem M.sacrospinalis und dem groβen Brustmuskelwie in Figur 1 angegeben. Zwischen 4 und 11 Rippen wurden entfernt-einschliesslich der Querfortsätze-bei 35 Kranken mit einem Todesfall. Die Ergebnisse der chirurgischen Therapie waren befriedigend.

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Studies on the Effects of Sympathicoamines in Asthma

Variability of Effect from Differing Routes of Administration*

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Introduction

This report on the use of sympathicoamines in bronchial asthma represents a portion of a continuing study of the effects of drugs on bronchial asthma,[1] using tests of ventilatory function as an objective measurement of airway obstruction.

We define asthma as a syndrome consisting of paroxysmal, recurrent and reversible partial obstruction of the lower bronchial tree resulting in the development of acute obstructive emphysema. Variability is a striking clinical feature of asthma both from patient to patient and in the same patient from day to day. The factors which produce bronchial obstruction in asthma are mucosal edema and congestion, bronchial inflammation, viscid secretion and bronchial muscle spasm. However, there is controversy regarding the relative importance of each one of these factors. From clinical observations it appears that the relative significance of these factors is not constant, but may be quite different in different patients, and may also show variation from time to time in any one patient. This accounts for the differing severity and response to treatment of asthma.

There is also no clear cut evidence as to the precise method by which epinephrine and the other sympathicoamines act to relieve human bronchial asthma. The antispasmodic action of epinephrine in relieving bronchial muscle spasm produced by vagal stimulation or drugs and the capillary constricting effects of epinephrine have been invoked.[2] Best and Taylor[2] and Goodman and Gillman[3] emphasize the antispasmodic effects of epinephrine. It has been pointed out[4] that epinephrine has a variable effect on bronchiolar musculature, depending on its tone. If the muscle is constricted, relaxation results. If it is relaxed completely, contraction of the muscle occurs. However, clinicians, such as Cooke,[5] Fineberg[6] and Lowell[7] emphasize the vasoconstrictive effects of epinephrine on congested and edematous bronchial mucous membrane. This study undertakes an evaluation of the results of differing routes of administration on the effectiveness of some sympathicoamines in relieving acute asthmatic episodes.

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Method

Patients were selected for study from the Allergy Clinic and from the emergency room of the hospital. No patient had received any type of medication for at least two hours prior to the study. Control determinations of the maximum breathing capacity and one second vital capacity were made using a nine liter Benedict Roth spirometer with soda-lime tower and valves removed. The one second vital capacity was calculated by measurement from the spirographic tracing. A fifteen second interval was used for the maximum breathing capacity, and the results were expressed in liters per minute at 37 degree centigrade, wet, ambient pressure. All measurements were repeated until good agreement between duplicate determinations for each test[1] was obtained and the largest measurement was recorded. Predicted values were calculated according to age, sex, height, and weight.[6] In analyzing the data, when the control maximum breathing capacity was less than 50 L/min., increases of maximum breathing capacity which were at least 20 per cent of the control value were considered significant. When the control maximum breathing capacity was more than 50 L/min., significance was ascribed to an increase in maximum breathing capacity of 10 L/min. or greater.[1]

The effect of sympathicoamine aerosols after a maximal bronchodilating effect of epinephrine subcutaneously.

On completion of control studies, the patient was given a subcutaneous injection of 0.3 mgm. of epinephrine and, after twenty minutes, the measurements were repeated. The patient was then given 0.2 mgm. of epinephrine subcutaneously, and after 20 minutes the studies were

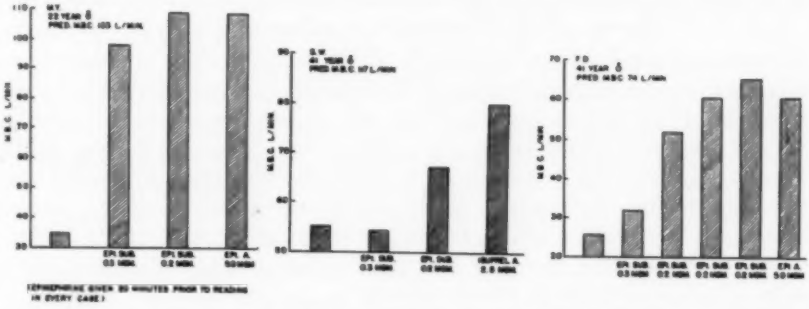

FIGURE 1: Response of bronchial asthma to repeated small doses of epinephrine subcutaneously.

The bars at the extreme left of each diagram represent the determined maximum breathing capacity and the control point before any drugs were given. The drug recorded beneath subsequent bars was given 20 minutes prior to that determination of the maximum breathing capacity. Patient M.Y. demonstrates an almost maximal response to a single subcutaneous injection of epinephrine. S.W. demonstrates no response to a first injection of epinephrine but significant responses to the second injection and a subsequent aerosol administration. F.D. demonstrates cumulative response to 4 injections of epinephrine. Abbreviations: epi for epinephrine; sub for subcutaneous; A for aerosol.

again repeated. The results of the measurements were then examined. If there was a significant change between the second and third maximum breathing capacity determinations, additional doses of 0.2 mgm. of epinephrine subcutaneously were given followed by repeat determinations of the maximum breathing capacity and one second vital capacity twenty minutes later until there was no significant change between two determinations. If there was no difference between the second and third maximum breathing capacity determinations, 5.0 mgm. of epinephrine or 2.5 mgm. of isoproterenol in 0.5 cc. of water was then given as an aerosol using a Vaponephrin nebulizer with compressed oxygen as the propellant. Twenty minutes later a final maximum breathing capacity and a one second vital capacity were determined. In 11 of 45 studies, the protocol was not completed in that the aerosol medication was given before a maximal effect of epinephrine subcutaneously had been demonstrated, and these studies are not included in the analysis of this portion of the data.

The effect of epinephrine subcutaneously after a maximal bronchodilating effect of sympathicoamine aerosol.

Eight studies were performed on six patients in which 0.3 mgm. epinephrine was administered subcutaneously after a maximum effect had been obtained with 0.5 per cent isoproterenol or 1 per cent epinephrine aerosol given as described above. Determinations of maximum breathing capacity and one second vital capacity were performed prior to drug administration and twenty minutes after each dose of medication.

Results

The effect of sympathicoamine aerosols after a maximum bronchodilating effect of epinephrine subcutaneously.

Forty-five studies were completed on 32 patients. Only the results of the maximum breathing capacity determinations are reported since an analysis of the one second vital did not appreciably alter the results. The control maximum breathing capacity was above 50 L/min. in 18 studies and below 50 L/min. in 27 studies indicating that, in general, the patients studied were having severe paroxysms of asthma. A significant response to sympathicoamine treatment occurred in 16 of the 18 studies where the control maximum breathing capacity was below 50 L/min. with a mean increase in M.B.C. of 22.5 L/min. There was a significant response in 22 of 27 studies in the group with control maximum breath-

TABLE 1 — RESPONSE OF THE MAXIMUM BREATHING CAPACITY TO EPINEPHRINE SUBCUTANEOUSLY

Studies showing significant rise after first injection	24
Studies showing no significant rise after first injection but a rise after second injection	8
Studies showing no significant rise after subcutaneous epinephrine	13
TOTAL	45

ing capacity above 50 L/min. with a mean increase in maximum breathing capacity of 30.0 L/min. This difference in mean increase of maximum breathing capacity is not statistically significant.

In 38 of the 45 studies, there was a significant improvement in the maximum breathing capacity at the end of the study as compared with the control point prior to the administration of any drugs. Seven studies failed to show an increase in the maximum breathing capacity despite repeated doses of sympathicoamines by both routes of administration. No patient was worse. It is of special interest that four of these seven studies were carried out on one patient, a 10 year-old girl with severe asthma of mixed allergic and infective etiology. The control maximum breathing capacities in this patient were 11, 41, 45, and 51 L/min. with a predicted maximum breathing capacity of 70 L/min. This variation of the control maximum breathing capacity indicates that airway obstruction was reversible although not responsive to sympathicoamines.

An analysis was made of the response to repeated subcutaneous doses of epinephrine (Table 1). In 24 studies, there was a significant response to the first injection of 0.3 mgm. of epinephrine. There was an additional response to subsequent injections of epinephrine subcutaneously in 10 of these 24 studies. In eight studies, a significant rise failed to occur on the first injection, but there was a significant response after a subsequent injection of 0.2 mgm. of epinephrine. Thirteen patients failed to respond to subcutaneous epinephrine, but six of the 13 did

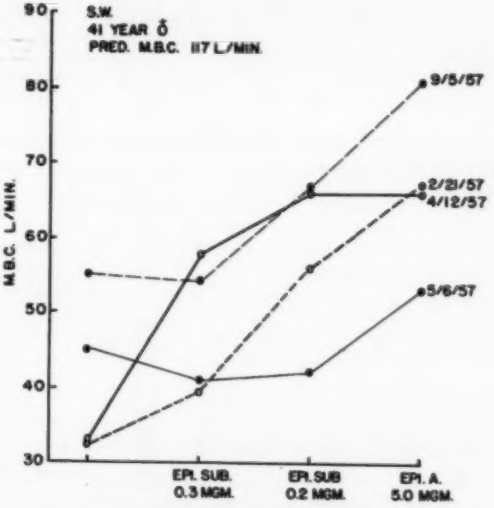

FIGURE 2: Variability of responses to epinephrine subcutaneously and by aerosol in a patient on four occasions during 1957.

On February 21, 1957 and April 12, 1957 there is a response to both of two subcutaneous injections of epinephrine. On May 6, 1957 no response to subcutaneous epinephrine is elicited, and on September 5, 1957 there is a response to only the second injection of epinephrine. Aerosol epinephrine produces a response on three of the four occasions.

TABLE 2 — COMPARISON OF AEROSOLS OF EPINEPHRINE AND ISOPROPYLATERENOL ON THE MAXIMUM BREATHING CAPACITY AFTER REPEATED DOSES OF EPINEPHRINE SUBCUTANEOUSLY

	Better	Worse	No Change	Total
Isuprel Aerosol	4	1	9	14
Epinephrine Aerosol	8	2	21	31

improve after sympathicoamine aerosol. Figure 1 presents typical examples of some of these responses. A cumulative effect of epinephrine subcutaneously is thus demonstrated in 18 of 45 studies.

Eight patients were studied on two or more occasions. Four patients showed a significant response to epinephrine subcutaneously on both occasions. Four patients failed to respond to epinephrine subcutaneously on one study but did respond significantly when studied on another occasion (Figure 2). This is interpreted as indicating variability in the bronchial pathology existing at the different observation points rather than variability in the pharmacologic properties of the sympathicoamines.

An analysis was made of the effects of isoproterenol aerosol as compared with the effect of aerosol epinephrine. The results are not considered to be significantly different (Table 2), and we therefore did not distinguish between isoproterenol and epinephrine aerosols in the analysis.

Thirty-four studies were performed in which it was demonstrated that maximum relief of airway obstruction had been obtained by the administration of repeated doses of epinephrine. Maximum effect of epinephrine subcutaneously was assumed to have occurred when there was no significant increase in the maximum breathing capacity between two doses.

A subsequent dose of aerosol epinephrine or isoproterenol caused a further significant rise in 10 patients, no further rise of maximum breathing capacity in 22 patients, and a significant fall in two patients

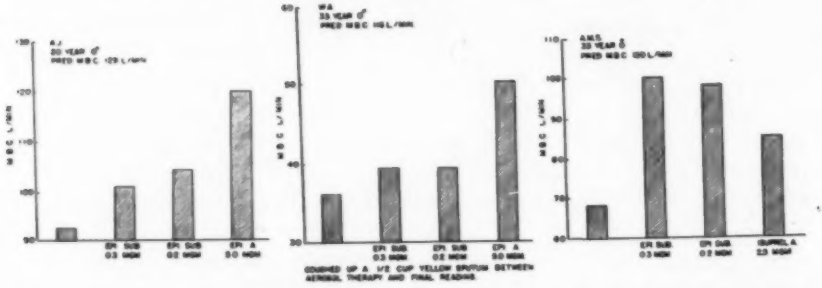

FIGURE 3: Effect of aerosolized sympathicoamines after a maximally effective dose of epinephrine subcutaneously.

A. J. and W. A. both show further rises after epinephrine aerosol. In W. A. the expectorant effect of the aerosol was likely an important factor in the rise of the maximum breathing capacity. Patient A.M.S. showed a significant fall in the maximum breathing capacity after aerosol isoproterenol.

TABLE 3 — EFFECT OF AEROSOLS OF EPINEPHRINE OR ISOPROTERENOL ON THE MAXIMUM BREATHING CAPACITY AFTER A MAXIMAL EFFECT HAS BEEN OBTAINED WITH EPINEPHRINE SUBCUTANEOUSLY

No further significant rise in Maximum Breathing Capacity	22 Studies
Significant rise in Maximum Breathing Capacity	10 Studies
Significant fall in Maximum Breathing Capacity	2 Studies
TOTAL	34 Studies

(Table 3 and Figure 3). Thus, in one-third of the patients sympathicoamines administered topically produced an effect which could not be elicited by sympathicoamines carried to the lungs and bronchi via the blood stream. The significance of this observation is discussed below.

The effect of epinephrine subcutaneously after a maximum bronchodilating dose of sympathicoamine aerosol.

In eight studies in which subcutaneous epinephrine was administered after a maximally effective dose of sympathicoamine aerosol (Table 4), there was a significant response to the aerosol and a further significant response to epinephrine subcutaneously in three studies. There was a significant response to aerosol and a fall after subcutaneous epinephrine in two studies and no significant response to aerosol or subcutaneous epinephrine in two studies. One study showed no significant response to aerosol, but a significant rise after subcutaneous epinephrine. As noted, two patients were studied twice in this group. The responses on initial and repeat study were the same in one patient but different in the other. Thus, in three of six studies in which reversible airway obstruction was demonstrated, a bronchodilator response could be elicited by subcutaneous epinephrine which could not be elicited by aerosol sympathicoamine.

Discussion

We have demonstrated an appreciable beneficial response to sympathicoamine therapy in 83 per cent of 53 studies. In 18 of the 45 studies a beneficial response was noted after a second subcutaneous injection of epinephrine. In 10 studies there was significant response on both the first and second injections. These studies confirm our clinical experience that epinephrine in repeated small doses often has a cumulative effect.

In 15 of 53 studies no benefit was obtained by the use of the sympathicoamines in repeated dosage either subcutaneously or by aerosol. We do not believe that this indicates "epinephrine fastness," if this term means the development of tolerance to epinephrine. Variability of the pathology seems to be a more likely explanation of

TABLE 4 — EFFECT OF EPINEPHRINE SUBCUTANEOUSLY ON THE MAXIMUM BREATHING CAPACITY AFTER MAXIMUM EFFECT OF SYMPATHICOAMINE AEROSOL

	No. of Studies
Significant response to aerosol and further significant response to epinephrine subcutaneously	3
Significant response to aerosol and fall after subcutaneous epinephrine	2
No significant response to aerosol; significant response to epinephrine subcutaneously	1
No significant response to either aerosol or subcutaneous epinephrine	2
TOTAL	8

the varying effectiveness of the sympathicoamines rather than a varying pharmacologic effect of these drugs. For exemple, if airway obstruction is primarily due to viscid adherent secretion and inflammatory infiltration, these drugs would have little effect. This concept is supported by our data showing variation in response to these drugs in 5 of 10 patients who were studied two or more times.

In 10 of 34 studies aerosolized drugs produced an effect which was additive to previously administered maximally effective doses of subcutaneous epinephrine. In three of six studies there was an additional response to subcutaneous epinephrine after a maximally effective dose of sympathicoamine aerosol. In one additional study there was no bronchodilation with the initial aerosol, but a significant response occurred with subsequently administered epinephrine subcutaneously. These findings are evidence that the effect of sympathicoamines may differ depending on the way in which they are administered. Aerosolized drug may have a more effective topical vasoconstricting effect, and the water vapor in the mist may have an effect in thinning mucus and permitting easier expectoration. Subcutaneously administered sympathicoamines may have a greater effect on vasoconstriction deep in the wall of the bronchus and on smooth muscle relaxation. Variation in response to administration of sympathicoamines by these routes in different patients and in the same patient at different times is probably due to differences in the pathology of the airway obstruction.

In two of our studies the patients were worse after aerosol therapy following benefit from subcutaneous therapy. The converse was also noted in two studies. Possible explanations of this are the well known rebound vasodilatation after epinephrine[3] and an irritating effect of the aerosol.

SUMMARY

Thirty-nine asthmatic patients have been studied following the administration of sympathicoamines either subcutaneously or as an aerosol on 53 occasions.

The failure of a patient to respond to epinephrine with relief of airway obstruction is not believed to be due to an alteration of the pharmacologic effects of the drug but is due to other causes of airway obstruction not affected by sympathicoamine action. Aerosolized sympathicoamines may have a greater vasoconstrictive effect in the superficial portions of bronchial mucosa. Subcutaneously administered sympathicoamines may have a greater effect on vasoconstriction deep in the bronchial wall and on lysis of bronchial muscle spasm.

These studies indicate the advisability of using sympathicoamines by both the subcutaneous and aerosol routes in the treatment of the patient with severe or refractory asthma. Small repeated subcutaneous doses of epinephrine often have a cumulative effect and have far fewer side effects than the same total dose of drug given as a single injection.

ACKNOWLEDGMENT: The technical assistance of Mr. Joseph Buck is gratefully acknowledged. The complete data, on which the tables are based, is available on request from the authors.

RESUMEN

Se estudiaron treinta y nueve asmáticos después de la administración de simpaticoaminas, ya sea subcutáneamente o por aerosol en 53 ocasiones.

La falta de respuesta del enfermo a la epinefrina con alivio de la obstrucción al paso del aire, se cree que no se debe a cambio en los efectos farmacológicos de la droga sino a otras causas de obstrucción que no son afectadas por la acción simpatiamínica.

Las simpaticoaminas pueden tener una acción vasoconstrictora mayor, en las partes superficiales de la mucosa bronquial.

Las simpaticoaminas inyectadas subcutáneamente, pueden tener mayor efecto vasoconstrictor y más profundo, en la pared bronquial y sobre la lisis del espasmo del músculo bronquial.

Estos estudios indican que es aconsejable el uso de las simpaticoaminas tanto por la vía subcutánea como por aerosol en el tratamiento de las asmas severas y refractarias.

Los dosis pequeñas y repetidas de epinefrina, a menudo tienen efecto acumulativo y tienen mucho menos efectos colaterales que la misma dosis total dada en inyección única.

RESUMÉ

39 malades asthmatiques ont été étudiés après administration de sympathicoamines donnés soit par voie sous-cutanée, soit 53 fois en aérosols.

Chez un malade, l'absence de réponse à l'épinéphrine avec soulagemen de l'obstruction des voies aériennes n'est pas dû, pense-t-on, à une altération des effets pharmacologiques du produit, mais à d'autres causes d'obstruction des voies respiratoires qui ne serait pas touchée par l'action du sympathico-amine. Des sympathico-amines en aérosols peuven avoir un effet vaso-constricteur plus grand dans les portions superficielles de muqueuse bronchique. Les sympathico-amines administrés par voie souscutanée peuvent avoir un effet plus marqué sur la vasoconstriction dans la paroi bronchique profonde et sur l'abolition du broncho-spasme.

Ces études montrent qu'il est indiqué d'utiliser les sympathico-amines à la fois par voie sous-cutanée et en aérosols dans le traitement d'un malade atteint d'asthme grave et réfractaire. De petites doses sous-cutanées répétées d'épinéphrine ont souvent un effet cumulatif, et ont de bien moindres effets toxiques que la même dose globale du produit donnée en une seule injection.

ZUSAMMENFASUNG

Beobachtungen an 39 Kranken mit Asthma im Anschluß an die Verwendung von sympathikomimetischen Mitteln, sei es subkutan, oder als Aerosol, bei 55 Gelegenheiten werden mitgeteilt.

Es wird die Auffassung vertreten daß, wenn ein Patient nicht auf Epinephrin mit Behebung des Atemhindernisses reagiert, dies nicht der Ausdruck einer Veränderung in der pharmakologischen Wirksamkeit des Medikamentes ist, sondern damit zusammenhängt, daß andere Ursachen für die behinderte Atmung vorliegen, die durch die sympathikomimetische Wirkung nicht betroffen werden. Vernebelte sympathikomimetische Mittel haben vielleicht einen stärkeren gefäßverengenden Effekt in den oberflächlich gelegenen Breichen der Bronchialschleimhaut. Subkutan gegebene sympathikomimetische Mittel können eine stärkere Wirkung ausüben auf die Gefäßverengung in der Tiefe der Bronchialwand und auf die Lösung des Spasmus der Bronchialmuskulatur.

Diese Beobachtungen zeigen die Zweckmässigkeit des Gebrauches von sympathikomimetischen Mitteln sowohl auf dem subkutanen wie dem Wegedes Aeresols zur Behandlung von Patienten mit schweren oder hartnäckigem Asthma. Kleine wiederholte subkutane Dosen von Epinephrin haben oft einen cumulativen Effekt und bringen weit weniger Nebenwirkungen mit sich als die gleiche Gesamtmenge der Substanz, wenn sie mit einer einzigen Injektion zugeführt wird.

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Effects of Pulmonary Hypertension of the Tracheobronchial Tree*

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While considerable material has been written on the inter-relationships of pulmonary and cardiac diseases, relatively little data have been recorded concerning changes in the major airways consequent to pulmonary hypertension.

Compression of the trachea by "vascular rings" is an exception to the foregoing statement and will not be covered herein. We are primarily concerned with those changes which occur in the tracheobronchial tree as sequelae to intrinsic diseases of the heart associated with pulmonary hypertension.

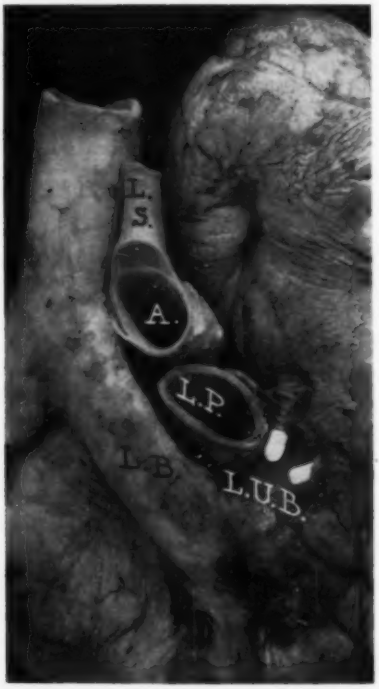

FIGURE 1: Anatomic relations of thoracic vessels and tracheal bifurcation. The trachea and section of the aorta and left pulmonary artery are viewed from in front. The aorta (A) lies adjacent to the trachea just above the bifurcation. The left pulmonary artery (L.P.) lies below the aorta and is bounded on the left by the left upper lobe bronchus (L.U.B.). Also shown are the left main bronchus (L.B.) and the left subclavian artery (L.S.). Probes appear in the left pulmonary veins.

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Some of these changes are of considerable interest to the academic anatomist, while others have a tangible bearing on the patient's symptomatology.

The types of pulmonary hypertension which affect the tracheobronchial tree may be separated, in general, into two categories, as follows: (1) those conditions in which the left atrial pressure is not elevated, and (2) those in which the left atrial pressure is elevated and in which the left atrial chamber is enlarged.

Pulmonary Hypertension Without Elevation of Left Atrial Pressure

Anatomically a relatively fixed space develops between the left side of the trachea and the left upper lobe bronchus and its branches. In this space lies the aorta and the proximal part of the left pulmonary artery (figure 1).

When the pulmonary arterial system is tense and distended from severe pulmonary hypertension, the left pulmonary artery has a tendency to push the aortic arch upward and to the right. As a consequence of this, the aortic indentation of the left side of the trachea may become more accentuated than is normal. In our experience this tracheal

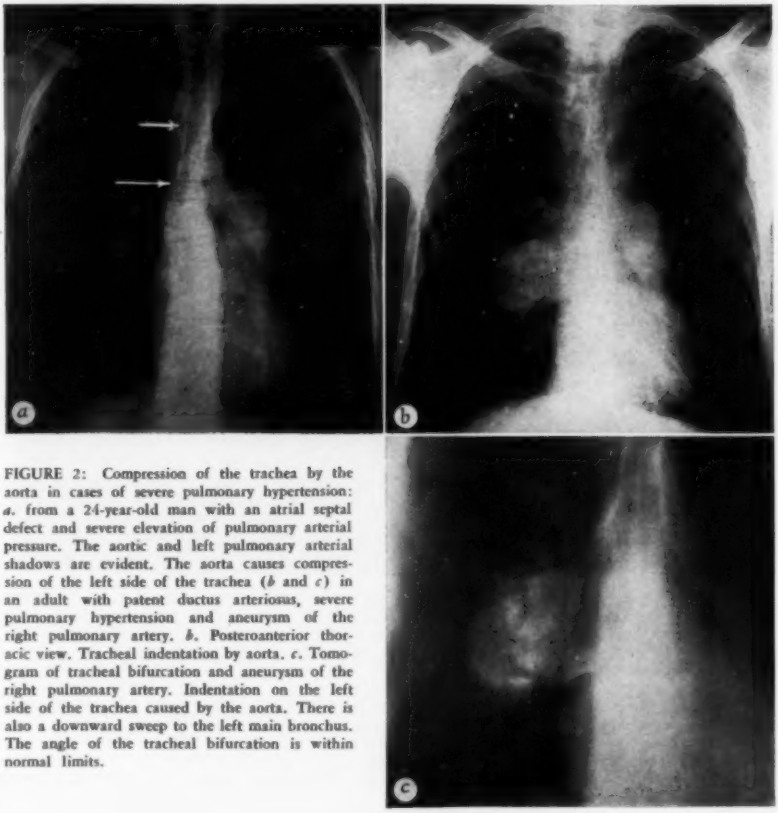

FIGURE 2: Compression of the trachea by the aorta in cases of severe pulmonary hypertension: *a*. from a 24-year-old man with an atrial septal defect and severe elevation of pulmonary arterial pressure. The aortic and left pulmonary arterial shadows are evident. The aorta causes compression of the left side of the trachea (*b* and *c*) in an adult with patent ductus arteriosus, severe pulmonary hypertension and aneurysm of the right pulmonary artery. *b*. Posteroanterior thoracic view. Tracheal indentation by aorta. *c*. Tomogram of tracheal bifurcation and aneurysm of the right pulmonary artery. Indentation on the left side of the trachea caused by the aorta. There is also a downward sweep to the left main bronchus. The angle of the tracheal bifurcation is within normal limits.

change has not been responsible for symptoms but, when identified in the clinical roentgenogram it is recognized as a reflection of increased pulmonary arterial pressure (figures 2 to 5).

Of interest is the surgeon's account of tense fullness in this region which has been observed during some operations for patent ductus associated with severe pulmonary hypertension in adults and of more easily defined component parts and increased room in the region when hypotension is induced.[1] Parenthetically, the process of pressure by the aortic arch against the trachea may cause impingement on the left recurrent laryngeal nerve and hoarseness. In one segment of its long course the left recurrent laryngeal nerve lies between the aortic arch and that part of the trachea which may be excessively indented under conditions of pulmonary hypertension.

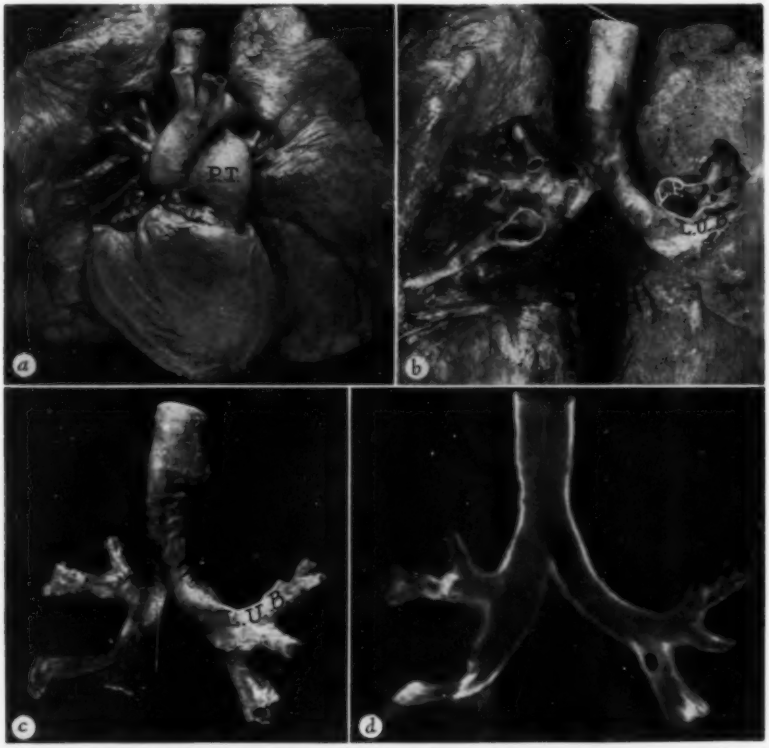

FIGURE 3: From 24-year-old man with atrial septal defect and severe pulmonary hypertension. *a*. The heart and lungs from in front. The pulmonary trunk (P.T.) is greatly dilated. *b*. Tracheal bifurcation viewed from front. The heart and aorta have been removed. There is indentation on the left side of the trachea which had been caused by compression from the aorta. The left pulmonary artery (L.P.) has been transected. The effects of the tense left pulmonary artery and of the aorta lying between the trachea and the left upper lobe bronchus (L.U.B.) have caused a downward sweep of the left main bronchus. *c*. The trachea and main bronchi from in front. The indentation on the left side of the trachea is apparent as is the broad downward sweep of the left main bronchus (L.U.B., left upper lobe bronchus). *d*. Trachea illustrated in *c*. Indentation on the left side of the trachea and the broad downward sweep of the left main bronchus.

Enlarged tense pulmonary arteries exert an indirect compressive effect on the trachea by way of the aorta and also may compress elements of the bronchi directly. This is particularly noticeable in the left main bronchus, which shows distortion downward and to the right, and results in a general broad downward concavity in this structure. In addition to the general effects, there may be localized indentation of the left main bronchus at the place of direct contact with the left pulmonary artery (Figures 3 and 5).

A second site of predilection for involvement is the bifurcation of the right main bronchus where the right lower pulmonary artery lies be-

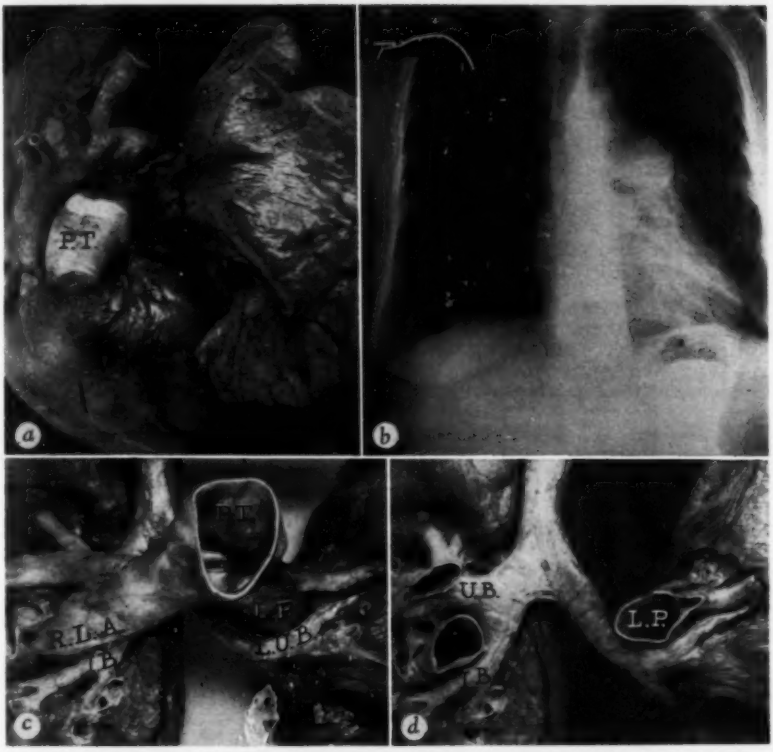

FIGURE 4: From an adult with patent ductus arteriosus and severe pulmonary hypertension. *a*. Front view of heart and lungs with advanced dilatation of the pulmonary trunk (P.T.). *b*. Posteroanterior view of thorax showing prominence of the pulmonary trunk and indentation of the trachea by the aorta. *c*. Tracheal bifurcation and the pulmonary trunk and its bifurcation. The pulmonary trunk (P.T.) has been pulled upward. The left pulmonary artery (L.P.) lies close to the left main bronchus and has caused a downward distortion of it (L.U.B., left upper lobe bronchus). The tense right pulmonary artery crosses in front of the right main bronchus. The lower lobe branch of the right pulmonary artery (R.L.A.) is in close relationship to the intermediate bronchus (I.B.) below and the upper lobe bronchus (out of view in this illustration) above. *d*. Tracheal bifurcation and pulmonary arteries. The left pulmonary artery (L.P.) has caused downward distortion of the left main bronchus. The lower lobe branch of the right pulmonary artery lies between the intermediate bronchus (I.B.) and the upper lobe bronchus (U.B.) causing an increase and rounding of the angle between these two structures and a compression, particularly of the intermediate bronchus. There is also flattening of the right bronchus and of the beginnings of its two branches.

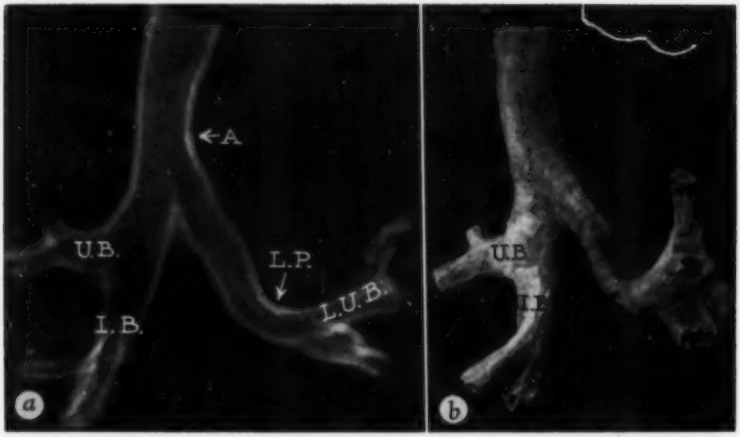

FIGURE 5: Same case as figure 4. *a*. Roentgenogram of the specimen of tracheal bifurcation showing indentation of the trachea by the aorta (A), downward displacement of the left main bronchus by the left pulmonary artery (L.P.). There are also a downward sweep of the left main bronchus and increase in the angle of the origin of the left upper lobe bronchus (L.U.B.) from the left main bronchus. The latter represents the effects of the enlarged left pulmonary artery. A rounding of the angle of bifurcation of the right upper lobe bronchus is also present as the right pulmonary artery had distorted the right upper lobe bronchus (U.B.) and the right intermediate bronchus (I.B.). *b*. The tracheal bifurcation viewed slightly from the left, showing the rounding of the angle of origin of the upper lobe and immediate bronchi from the right main bronchus. The downward displacement of the left main bronchus by the left pulmonary artery is clearly apparent. From this view the indentation on the left side of the trachea is shown slightly.

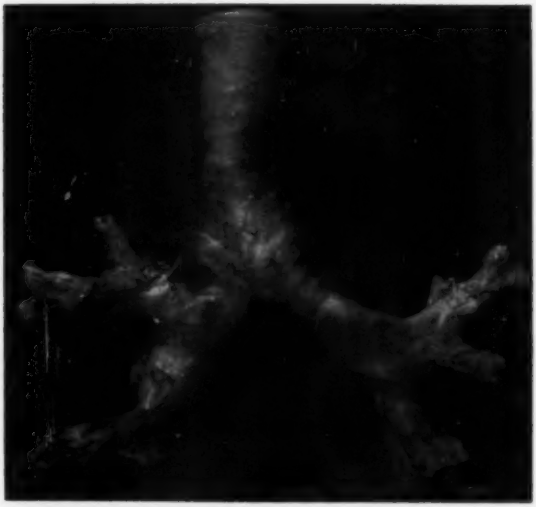

FIGURE 6: Tracheal bifurcation in 24-year-old man with atrial-septal defect and pulmonary hypertension (same case as in figure 2*a* and 3). Specimen viewed from front. In addition to the features which have already been described for this case, the intermediate bronchus shows compression from above downward which has been caused by the tense and enlarged right lower lobe artery.

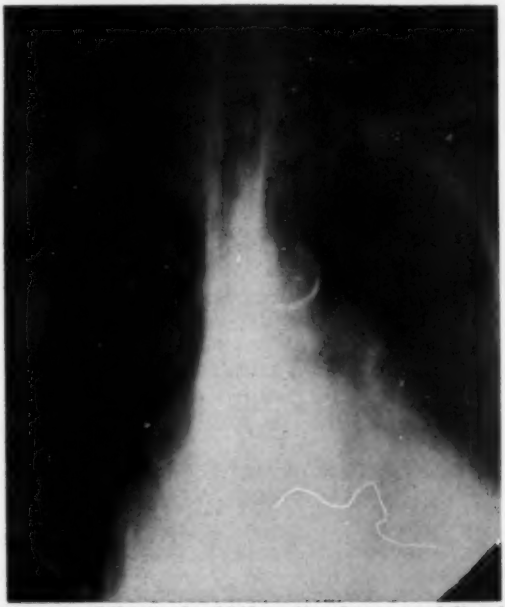

FIGURE 7: Tomogram of the tracheal bifurcation from an adult patient with mitral stenosis. The aorta (calcified) compresses the trachea and causes slight indentation along its left aspect. In this regard pulmonary hypertension associated with left atrial pressure is similar to that which occurs without elevation of left atrial pressure. A difference, however, exists, in that in association with elevation of left atrial pressure the tracheal bifurcation may show increased angulation mainly from upward displacement of the left main bronchus, as illustrated.

FIGURE 8: Anatomic relations of the tracheal bifurcation to the left atrium. The specimen viewed from behind. The upper portion of the left atrial cavity is shown. The tracheal bifurcation arches over the left atrium (L.B.=left main bronchus. R.B. =right main bronchus). The aorta (A) has been divided as it lies beside the trachea at the region where the arch turns down to the descending aorta. The left pulmonary artery (L.P.A.) ascends in front of the left main bronchus and passes downward posteriorly to the left upper lobe bronchus (obscured from view by the artery in this perspective). The left upper pulmonary vein (L.U.P.V.) lies in front of and inferior to the left main bronchus. The left main bronchus therefore lies between the left pulmonary artery above and the left upper pulmonary vein in front and this vein and the left atrium, below.

tween the right upper lobe bronchus above, the intermediate bronchus below, and the distal end of the right main bronchus to the left. The tense, dilated right lower pulmonary artery may push each of the two bronchial branches away from each other and compress them as well (figures 5 and 6).

Pulmonary Hypertension with Elevation of Left Atrial Pressure

When the left atrial pressure is elevated and the left atrium enlarged, additional mechanical influences are placed on the tracheobronchial tree to those which exist when pulmonary hypertension is not associated with elevation of left atrial pressure. It is evident that when the left artial pressure is elevated, pulmonary arterial hypertension coexists. From this feature, the same qualitative influences on the tracheobronchial tree exist as outlined in the foregoing section, to which is added displacement of the structures by the atriomegaly.

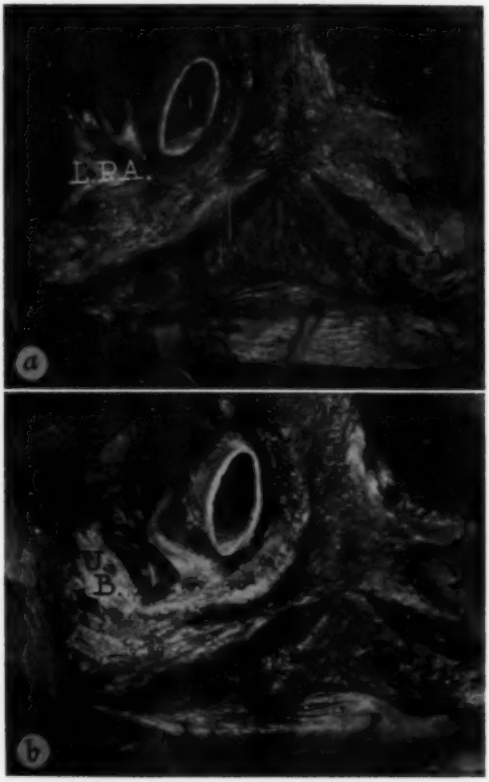

FIGURE 9: Anatomic relations of the tracheal bifurcation (same perspective as in figure 8). The left pulmonary artery hooks around the left upper lobe bronchus in the shape of a Roman arch. This anatomic arrangement tends to prevent upward deviation of the left main bronchus. *a*. The left pulmonary artery (L.P.A.) arches behind the left upper lobe bronchus and obscures the left upper lobe bronchus from view. *b*. A segment of the left pulmonary artery has been removed exposing the left upper lobe bronchus (L.U.B.) from this, the posterior, view.

It is noteworthy, however, that when pulmonary arterial hypertension exists in association with elevated left atrial pressure, the effects on the major airways by the enlarged left atrium may be at least as pronounced as those caused by the altered pulmonary arteries (Figure 7).

Review of several anatomic relations of the left atrium and the tracheal bifurcation may serve to explain the observed changes.

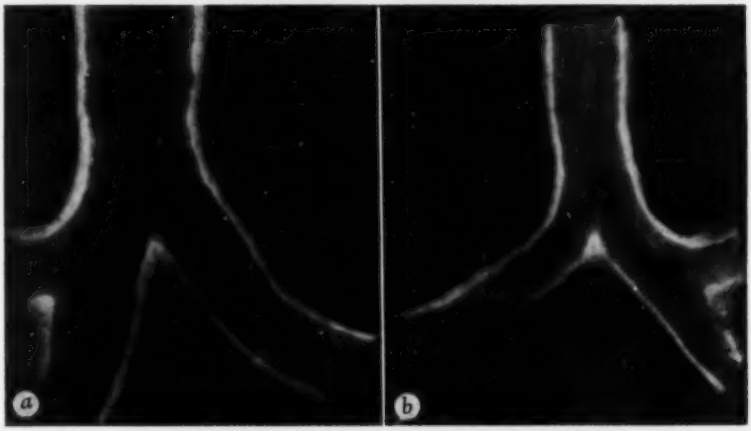

FIGURE 10: Tracheal bifurcation viewed from behind. *a*. From a normal. *b*. From a patient with mitral insufficiency and enlargement of the left atrium, showing the increase in angle of the tracheal bifurcation as compared with the normal shown in *a*. (From Burchell and Edwards, "Rheumatic Mitral Insufficiency," *Circulation*, 7:747-756 [May] 1953.)

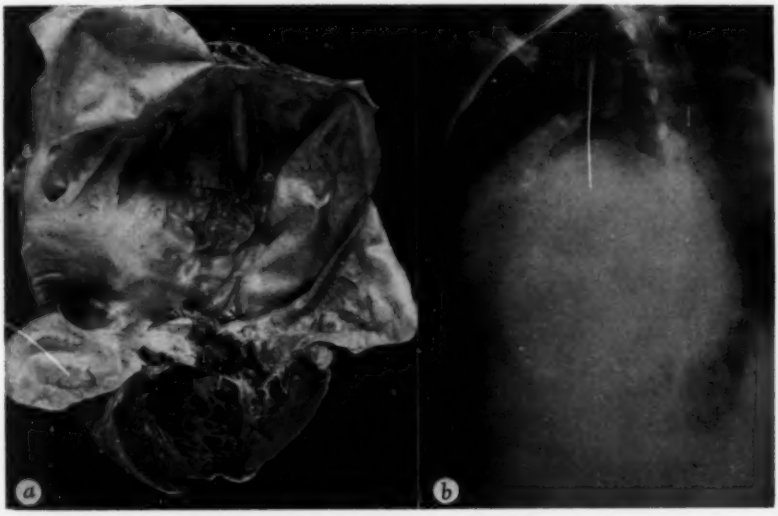

FIGURE 11: Increased angulation of the tracheal bifurcation in an adult with acquired mitral insufficiency. *a*. Left side of heart, the mitral valve was the site of recent surgical intervention. The left atrium is of giant proportions. *b*. Left anterior oblique view of thorax shows the large increase in angle of the tracheal bifurcation which now approaches 180 degrees.

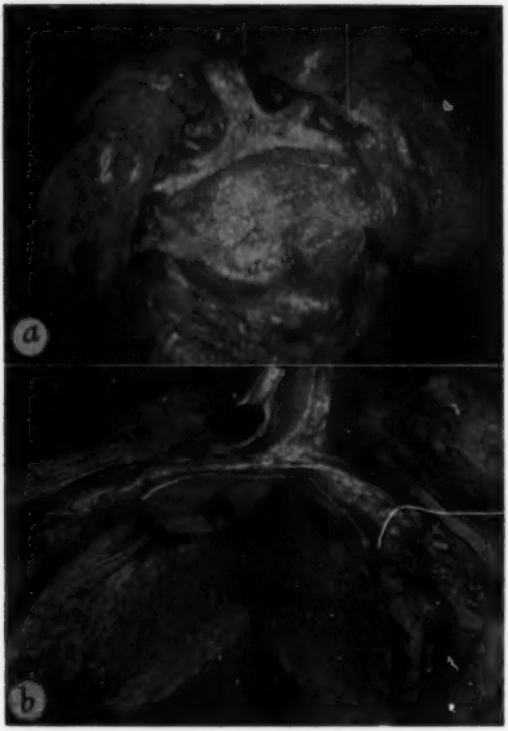

FIGURE 12: Distortion of tracheal bifurcation by enlarged left atrium. *a*. Heart and lungs from behind in an adult with mitral insufficiency. The left atrium is large. The angle of the tracheal bifurcation approaches 180 degrees. *b*. Compression of the left main bronchus in enlargement of the left atrium. View from behind. The increase in angle of the tracheal bifurcation is pronounced. The sharp posterior edge of the left main bronchus is evidence of compression (see fig. 13*c*). (From Burchell and Edwards, "Rheumatic Mitral Insufficiency," *Circulation*, 7:747-756 [May] 1953.)

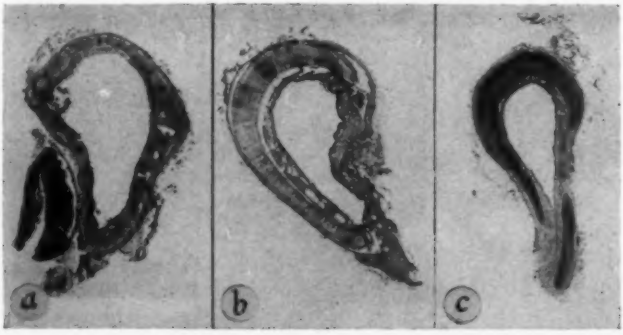

FIGURE 13: Low-power photomicrographs of left main bronchi from a normal person and two patients having enlargement of the left atrium. *a*. The normal bronchi. *b*. Mild compression, particularly advanced along the noncartilaginous portion of the bronchus. *c*. Profound compression causing distinct change in contour and size of the lumen of the bronchus. (*a* and *c* from Burchell and Edwards: "Rheumatic Mitral Insufficiency," *Circulation*, 7:747-756 [May] 1953.)

The two major bronchi arise from the tracheal bifurcation arch over the superior aspect of the left atrium (figures 8 and 9). The left main bronchus lies above the left atrium and more closely above the left pulmonary veins as they enter the left atrium. The left pulmonary artery lies in front of the left main bronchus as it courses upwards. After reaching the level of the upper aspect of the bronchus the artery then arches downward behind the left upper lobe bronchus. In its relation to the left upper lobe bronchus the left pulmonary artery may be described as having the shape of a Roman arch and tends to hold the whole left bronchial system downward as it passes over the left upper lobe bronchus (figure 9).

As the left atrium enlarges from disease, the angle of the tracheal bifurcation increases, as was described in 1929 by Steele and Paterson.[3] In normal anatomic specimens the angle of the normal tracheal bifurcation is usually about 90 degrees. In cases of extreme left atrial enlargement, this angle may be increased to almost 180 degrees, so that the long axes of the two bronchi may lie close to the same horizontal plane (figures 10, 11 and 12). The upward pressure by the enlarged left atrium against the lower aspect of the major bronchi has a tendency to compress the bronchi and facilitate collapse, while the deviation of the bronchi upwards from their usual position tends to avoid this effect. The right main bronchus rarely, if ever, shows any significant compression. The left main bronchus, on the contrary, may show considerable compression (Figures 12*b* and 13).

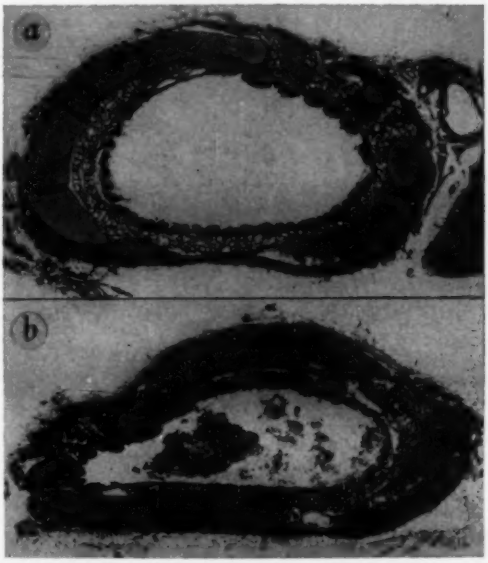

FIGURE 14: From a 2½-year-old child with total anomalous pulmonary venous connection to the coronary sinus in which the coronary sinus formed a chamberlike recess posterosuperior to the left atrium. The child had suffered from recurrent pulmonary infection. *a*. Right main bronchus; the contour is essentially normal (hematoxylin and eosin; x10). *b*. The left main bronchus. Luminal narrowing from compression. The lumen contains exudate (hematoxylin and eosin; x10).

Compression of the left main bronchus seems to be a result compounded by several functional and anatomic effects.

From the foregoing anatomic consideration it is apparent that under conditions of increased left atrial size, two opposing forces are exerted on the left main bronchus. The enlarged left atrium and left pulmonary veins tend to push the bronchus upward, while the left pulmonary artery tends to prevent this deviation in position. The ultimate effect is a compression of the left main bronchus.

In adult patients, ordinarily, compression of the left main bronchus is not readily correlated with symptoms. In infants and children this process may be responsible for obstructive emphysema or atelectasis and recurrent pulmonary infection (figures 14, 15 and 16).

The greater tendency for children and infants to exhibit pulmonary symptoms as a result of bronchial compression may stem from the facts that children, who have an intrinsically small airway, may reach a critical point more readily than adults, who have larger airways, and that the greater pliability of the bronchial cartilage of children may make compression more likely than the more rigid cartilages of adults.

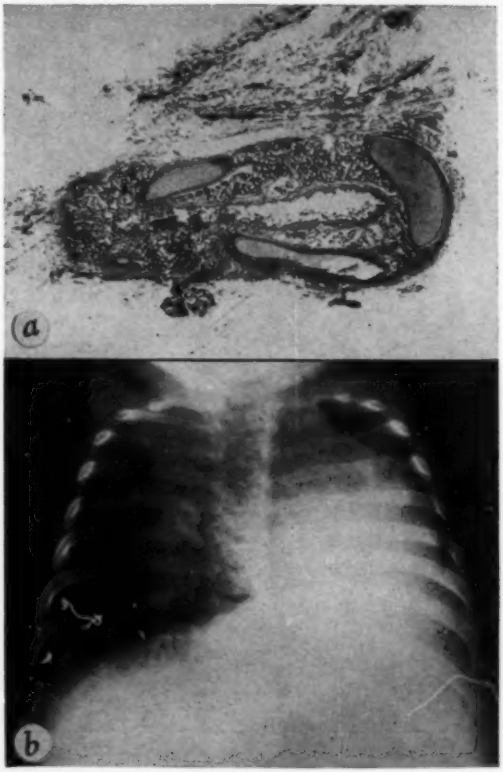

FIGURE 15: From a 5-month-old child with ventricular septal defect, a large left-to-right shunt and enlargement of the left atrium. The patient had suffered from recurrent pulmonary infection associated with bronchial compression. *a*. Compressed left main bronchus (hematoxylin and eosin; x10). *b*. View of thorax.

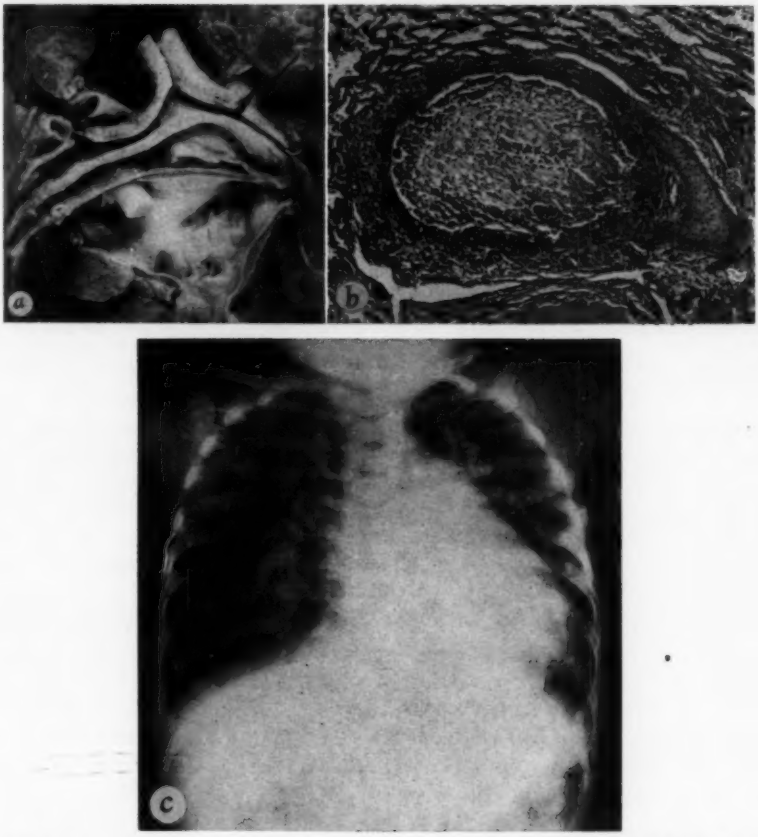

FIGURE 16: From an 8-month-old infant with ventricular septal defect, a large left-to-right shunt and enlargement of the left atrium. Recurrent pulmonary infection from bronchial compression and accumulation of mucus had developed. *a*. Posterior view of tracheal bifurcation and left atrium. The angle of the tracheal bifurcation is increased. The left main bronchus is compressed. Probe lies in left upper pulmonary vein. The left pulmonary artery, which arches over the left upper bronchus, has been divided in the specimen. *b*. Specimen from lower lobe of left lung showing a small bronchus filled with exudate composed of neutrophils and mucus. Widespread accumulations of this type were considered to be the cause of recurring pulmonary infection in this infant (hematoxylin and eosin; x100). *c*. View of thorax.

Histologically the cartilages of compressed bronchi do not show intrinsic disease that would tend to make permanent changes even after the course of the compression is removed.

From greater experiences with tracheal compression by vascular rings, it is apparent that deformities of the major airways in children may remain long after the cause is removed or corrected.

At present it is unknown whether the exact basis for ultimate improvement is the intrinsic correction of cartilaginous deformity or the adjustments that are associated with body growth.

SUMMARY

Pulmonary hypertension associated with cardiac disease may effect distortions and compressions of the tracheobronchial tree. Certain changes result from pulmonary

arterial hypertension alone. When elevation of left atrial pressure also is present, additional deformities occur. In children, the compressive effects of hypertensive pulmonary vessels may cause significant pulmonary complications.

RESUMEN

La hipertensión pulmonar asociada con enfermedad cardiaca, puede causar distorsiones y compresión del árbol traqueobronquial.

Ciertos cambios resultan de la hipertensión pulmonar sola.

Cuando la elevación de la presión atrial izquierda también se encuentra, el efecto compresivo de los vasos pulmonares hipertensos, puede ocasionar complicaciones pulmonares de significación.

RESUMÉ

L'hypertension pulmonaire liée à une affection cardiaque peut provoquer des distorsions et des compressions de l'arbre trachéobronchique. Des altérations incontestables proviennent de la seule hypertension artérielle pulmonaire. Lorsqu'on constate également une élévation de la pression de l'oreillette gauche des déformations supplémentaires surviennent. Chez les enfants, les effects compressifs des vaisseaux pulmonaires hypertendus peuvent provoquer des complications pulmonaires importantes.

ZUSAMMENFASSUNG

Pulmonale Hypertension in Verbindung mit Herzerkrankung kann zu Distorsion und Kompressionen des Tracheobronchialbaumes führen. Gewisse Veränderungen rühren ausschliesslich vom pulmonalen arteriellen Hochdruck her. Liegt auch ein arhöhter Druck im linken Vorhof vor, kommt es zu zusätzlichen Deformitäten. Bei Kindern können die komprimierenden Wirkungen überstark gespannter Lungengefässe beträchtliche pulmonale Komplikationen bewirken.

REFERENCES

1 Kirklin, John W.: "Personal Communication to the Authors."

2 Steele, J. M., Jr., and Paterson, Ralston: "Distortion of the Bronchi by Left Auricular Enlargement," *Am. Heart J.*, 4:692, 1929.

Recognition of Early Emphysema by Pulmonary Function Tests*, **

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Chronic obstructive emphysema has been fully accepted as an increasingly common pathologic condition of the lungs. Though well recognized, this disease has given rise to diverse theories concerning its origin. The proposed etiologies run the gamut from congenital lack of elastic fibers, diminished circulation, chronic bronchitis, bronchiectasis, silicosis, tuberculosis, asthma and chemical irritants to smoking. The pathology seems confused by lack of definition, and difficulty in quantitating degrees of emphysematous impairment. The physiologists have studied far advanced emphysema extensively and have amply documented the gross changes such as obstruction of airways, uneven distribution of inspired air, increased lung volume, abnormal ventilation blood flow ratio, reduction in vascular bed, poor diffusion and altered blood gases. This paper is concerned with the application of pulmonary function tests in the detection of early emphysema.

Recognition of early emphysema is essential for the proper study of the natural history of this disease. If we are, indeed, to incriminate such items as chronic bronchitis, and smoking, the disease must be evaluated throughout its course. Those who wait for physiologic tests to indicate far advanced disease will miss the most crucial phase of the disease, namely the onset. As a general principle, little is learned about a pathologic condition by studying the late stages of disease. Furthermore, from the point of view of control of emphysema, one must ameliorate the condition before dyspnea becomes a prominent symptom.

How does one recognize early emphysema by pulmonary function tests? First, we will examine the tests used for recognition of far advanced disease and determine whether or not they are applicable to the problem. Emphysma, when most advanced, causes CO_2 retention and respiratory acidosis, but in the earlier stages this does not occur. Likewise, arterial blood oxygen unsaturation is a late finding. Bates, Knott and Christie[1] and others have reported that reduced diffusing capacity is a poor prognostic sign but again this finding is observed late in the course of the disease. Most often an increase in residual volume has been considered essential for making a diagnosis of emphysema,[2] but this too is a late manifestation. By a process of elimination we are now reduced to a discussion of the several ventilatory tests. Such a battery might be particularly useful clinically because ventilatory tests are easy to perform. To use many of these may be misleading because of their variability in emphysema.[3] Those who treat patients with asthma, for instance, recognize that the ventilatory tests may revert toward normal as the dis-

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ease improves. Is it possible to selectively choose ventilatory tests which will minimize these objections?

The vital capacity (VC) is the best known of the ventilatory tests. In emphysema, it may be normal in the early stages, increased in the moderately advanced stage and only significantly decreased in the late stage. However, this relationship is not a constant finding and the vital capacity is not considered discriminatory in early disease.

From the standpoint of physical examination one of the prominent features of emphysema is the prolonged expiration time. This can readily be measured by timed vital capacity (TVC).[4] This test should be included in our proposed battery of tests. The maximum breathing capacity (MBC) closely correlates with TVC in the obstructive type of breathing and therefore will add little except in the interpretation of the spirogram. The MBC has a limitation similar to the VC because it also may be in the normal range in early emphysema.

The air trapping indicated by elevation of the MBC spirogram E, has received little emphasis in physiologic literature, perhaps because the cause of this phenomenon remains obscure. Whittenberger[5] ascribes the air trapping to increased resistance in the airways which causes a step like increase in trapping "until lung volume equilibration occurs at a point when the added pressure drop (resistance) is counter balanced by the increased potential energy of the lung at the end of inspiration." Figure 1a shows a typical MBC spirogram with progressive air trapping to hyperinflation level. On the other hand, many patients when asked to breath rapidly and deeply, as during exercise or performing the MBC, will first hyperinflate the lungs, to the limit of their inspiratory capacity as illustrated in Figure 1b. Even patients with early emphysema, custom-

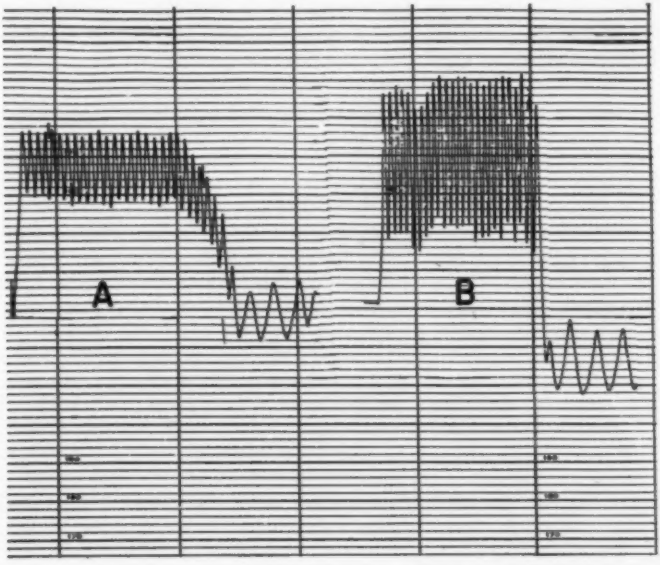

FIGURE 1: Maximum breathing capacity spirograms. (a) Step wise elevation to hyperinflation level. (b) Abrupt rise to hyperinflation level.

arily take one or more deep breaths before beginning rapid breathing, just as though about to plunge into a cold pool of water. The reason for this maneuver of hyperinflation is not clear. Perhaps, it is a habit acquired at an early age, or the psychosomaticist might suggest an anxiety phenomenon. More likely this maneuver improves the mechanics of the lung by placing the elastic tissue on the stretch, improving compliance and reducing airway resistance. This phenomenon of air trapping is a constant early finding in emphysema and is not abolished by administration of bronchodilators. Generally, the more rapidly the MBC is performed the higher the level of hyperinflation up to the limit of the inspiratory capacity. It should be noted that a few patients with very low inspiratory capacity may be unable to trap air.

The normal lung has remarkably uniform gas distribution, but the emphysematous lung has uneven ventilation. When one inspects the freshly cut section of an emphysematous lung (Fig. 2) or the whole lung section prepared by the Gough technique,[6] one can detect with the unaided eye the diffusely enlarged alveoli or confluent spaces formed by the breakdown of alveolar septi. These spaces vary in size and have communicating ducts of diverse sizes. It seems reasonable to expect, therefore, that the distribution of gases within such lungs may be abnormal. The single breath of O_2 test (SB) described by Comroe and Fowler[7] is recommended for measuring uneven ventilation within the lungs and is included in our proposed group of tests.

Thus, three simple ventilatory tests are available, each measuring a different facet of the complex pathologic physiology of the emphysematous lung. The TVC gives information on the degree of obstruction of the air flow. The elevated MBC spirogram reveals evidence of air trapping within the lung. Finally a rising alveolar nitrogen curve after a single

FIGURE 2: J.H.G. age 54. Right upper lobe showing diffuse early emphysema. The three ventilatory tests were positive.

breath of O_2 suggests the presence of uneven distribution of gases within abnormally large alveolar spaces. A preliminary study from this laboratory showed that when a combination of each of these three tests which measure three different parameters of the lung are abnormal, then the presence of early emphysema may be diagnosed with considerable accuracy.[8] The investigation concerning the detection of early emphysema was carried out on 328 consecutive patients who had pulmonary resection. The specimens removed varied from single segments up to complete pneumonectomies. The purpose of the present study was to enlarge our experience by correlation of these tests with the pathologic findings in 150 patients undergoing lobectomy for removal of tuberculous lesions.

Material and Methods

One hundred and fifty tuberculous patients in whom lobectomies may be considered to yield "ideal biopsies" were selected. Patients in whom the entire lobes were destroyed by disease or compressed under thoracoplasty or plombage were excluded because such specimens do not offer representative samples of lung tissue. The fresh lung specimens were inflated to normal size with formalin solution and several days later cut in slices approximately 1.0 cm. in thickness. Emphysema was considered to be present when generalized diffuse enlargement of the alveoli was apparent to the unaided eye. Colored photographs were taken and slides made which demonstrated *diffuse* emphysema (Fig. 2) with great clarity when projected on a large screen. In contrast, (Fig. 3) shows a section of lung with focal emphysema at the apex, the remaining portion appears to be normal lung tissue. Histologic confirmation was not attempted. Emphysema in conjunction with tuberculosis has received little attention from pathologists and usually in far advanced cases. There seems to be agreement, however, on two forms of emphysema; one generalized emphysema which may or may not be related to tuberculosis and secondly focal which is closely associated with tuberculous lesions.[9] The latter type may involve lung tissue surrounding the distortion caused by disease or appear peripherally in which case bullae also may be noted.[10]

TABLE 1 — COMPARISON OF NONEMPHYSEMA WITH EMPHYSEMA PATIENTS BY DECADES IN RELATIONSHIP TO VENTILATORY TESTS

					Recommended Screening Tests						
		No.	Av. Ht.	Av. Wt.	Av. TVC 2 Sec. per cent	Av. SB per cent	No. Pts. With No E	No. Pts. With E	Av. MBC per cent	Av. VC per cent	Av. TR per cent
20-29 Years	No Emphysema	21	71	159	93	0.7	16	5	103	101	4.9
	Emphysema	5	70	136	72	2.0	0	5	72	80	10.0
30-39 Years	No Emphysema	42	69	156	87	1.2	21	21	97	100	6
	Emphysema	13	69	150	80	2.8	4*	9	70	78	10.6
40-49 Years	No Emphysema	20	69	155	84	1	16	3	105	103	6.5
	Emphysema	20	69	148	72	2.4	2**	18	91	98	7.3
50 or More	No Emphysema	10	68	149	83	1.1	10	0	105	108	5
	Emphysema	19	67	139	71	3.1	1	18	80	94	7.3

*2 had low inspiratory capacity
**1 had low inspiratory capacity
See text for symbols

Each patient received pulmonary function tests within two weeks before lobectomy. Ninety-four of the 150 patients were available for testing at an average period of six months postoperatively. Vital capacity was performed on a 13.5 liter Collins respirometer by the method of Baldwin.[3] Timed vital capacity was carried out on a 7 liter Collins vitalometer fitted with a potentiometer to transcribe the record on electrocardiographic paper.[11] Maximum breathing capacity was determined on a 13.5 liter Collins respirometer by the method of Baldwin[3] and the spirogram was inspected for evidence of air trapping. The single breath O_2 test for uneven ventilation was carried out by our modification[13] of the method of Comroe.[7] Residual volumes (RV) and index of intrapulmonary mixing by the open circuit method[13] were determined in 20 patients with grossly abnormal screening tests.

Results

Data on the 150 tuberculous patients are presented in Table 1. The patients are divided into decades and each decade is subdivided into two groups according to whether or not emphysema was noted in the gross lung sections. As might be expected, there are more patients in the older age groups who have emphysema. Two factors may be operating here: it is recognized that the incidence of emphysema increases with age and the older patients have had pulmonary tuberculosis for greater lengths

FIGURE 3: L.M. age 33. Right upper lobe showing focal emphysema in apical segment. The 2 second TVC was 83 per cent, the MBC spirogram normal, S.B. 1 per cent but the TR was 9 per cent indicating localized areas of poor gas distribution.

of time. The patients in each decade who had emphysema have a significantly lower weight than the nonemphysematous patients. In the emphysematous groups the VC and MBC tend to be lower but are not satisfactory for the detection of emphysema because of the wide range of values in the nonemphysematous group due in part to the variation in the pulmonary involvement with tuberculosis. Average vital capacity is 102 per cent, range 61 per cent to 142 per cent. Average maximum breathing capacity is 101 per cent range 48 per cent to 153 per cent. It may be seen in Table 1 that elevation of the MBC spirogram, on the other hand, gives a rather sharp demarcation between the normal and abnormal, particularly in the older age group. Timed vital capacity behaves in the reverse manner, namely better discrimination occurs in the younger age groups where the average 2 second TVC for the nonemphysematous in the age 20-29 is 93 per cent but reduced to an average of 83 per cent in the age group 50 or over. It is demonstrated that the single breath test does not significantly increase with age in our nonemphysematous groups. This finding is not in accord with the results of Comroe's studies,[7] but comparison may not be entirely valid because our patients were not normal subjects. Finally, the terminal rise (TR) values are not discriminatory because in nonemphysematous patients there may be elevation in a variety of conditions such as open cavities, blebs, bronchiectasis, pleural adhesions and impaired function of the diaphragm. It may be seen, nevertheless, that in general the emphysematous patients have a higher TR as previously reported.[14]

Figure 4 shows the results of the combination of the three screening tests, TVC, elevation of MBC spirogram and SB. The criteria used in detecting emphysema in these 150 tuberculous patients were: 2 second TVC of 90 per cent or less, elevation of th MBC spirogram above the resting expiratory level, and SB test of 2 per cent or greater. It may be seen that there are 93 patients without demonstrable emphysema in the sections of removed lobes. There were two patients in whom the combined tests indicated emphysema, although none was demonstrated pathologically. Fifty-seven patients had emphysema shown by the "ideal biopsy." The results of the combined function tests correctly indicated emphysema in 49 and failed to be definitive in eight of these patients. The three ventilatory tests were correct in indicating whether or not emphysema was present in 93 per cent of the patients.

Discussion

It is well known that the use of ventilatory tests to indicate emphysema in the asthmatic patient may be unreliable unless the examinations are made when the

TABLE 2 — TIMED VITAL CAPACITY CUT OFF VALUES AND MEDIAN VALUES BETWEEN NONEMPHYSEMATOUS AND EMPHYSEMATOUS PATIENTS

TVC	Best TVC Cut Off Values		TVC Per cent Correct	Median
1 second	73 per cent	Emphysema	91 per cent	62
		No Emphysema	50 per cent	73
2 second	89 per cent	Emphysema	93 per cent	75
		No Emphysema	52 per cent	89
3 second	93 per cent	Emphysema	91 per cent	82
		No Emphysema	54 per cent	93

patient is in an asthmatic free period and has achieved maximum improvement with effective bronchodilator drugs prior to testing. Similarly it might be argued that as the tuberculosis becomes inactive the three recommended screening tests might revert to normal. It should be noted that these patients were, for the most part, x-ray stable and under antibiotic therapy for many months before being subjected to lobectomy—some, however, had cavitary type of resection and still had positive cultures for acid fast bacilli (AFB). Information regarding the reversibility of the tests may be obtained by follow-up studies. Ninety-four of these patients were available for retesting at an average period of six months following lobectomy. There were six patients in the non-emphysematous group who, after surgery, appeared to develop emphysema by these tests. One reverted from a false positive to negative. In the emphysematous group, two patients had negative results on preoperative pulmonary function testing which became positive after operation. Only one patient in the emphysematous group reverted back to normal tests after surgery. Thus it becomes quite clear that reversibility of the tests is infrequent in patients with stable tuberculosis lesions.

In the previous study,[8] the 2 second TVC was selected as showing better discrimination than the 1, or 3 second tests. Bernstein[15] has demonstrated that there is no advantage of one particular time over another since they all arise from similar curves. He showed that correlations between 1, 2 and 3 second timed vital capacities were equally good when compared with MBC. Tabulation of TVC data from these 150 patients tends to confirm Bernstein's concept. Table 2 shows that the cut off values between emphysema and nonemphysema fall at the level of 73 per cent for 1 second, 89 per cent for 2 seconds, and 93 per cent for 3 seconds. Using these cut off points, the 2 second TVC was slightly higher in discrimination. When the median values for the TVC for emphysematous and nonemphysematous groups were calculated it was found that the 2 second TVC provided values slightly farther apart and thus produced better discrimination. The differences are slight between the 1 second, 2 second and 3 second but the results of this study again favor the 2 second with 89 per cent as the level at or below which emphysema may be suspected.

Tabulation of the values for the single breath test show that the best cut off level is at 2 per cent. Values above this level are also considered to be abnormal by Comroe.[7]

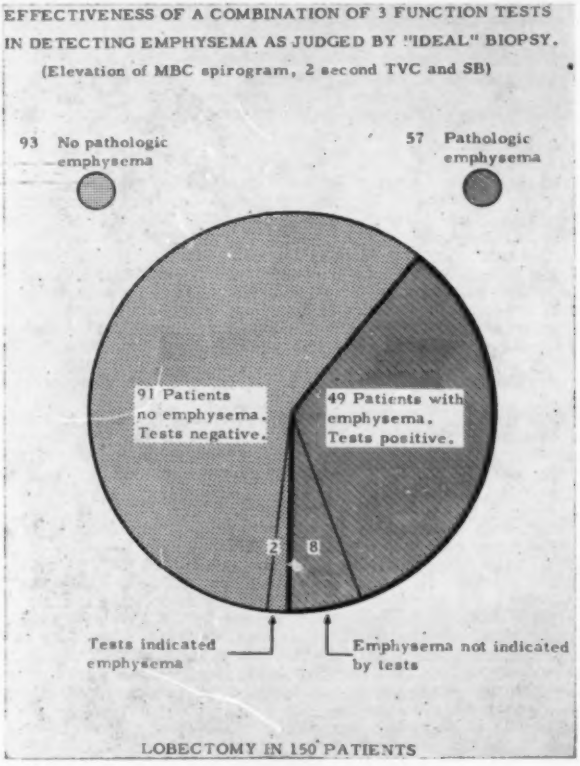

FIGURE 4

The ratio of residual volume over total lung capacity (RV/TLC x 100) is thought to be abnormal if above 35 per cent although this value increases with age as was demonstrated by Gilson.[16] Baldwin[2] has stated that the diagnosis of emphysema should not be entertained unless the ratio of RV/TLC x 100 is 35 per cent or greater. In our study the ratio was determined in 20 patients having the most abnormal screening tests. Only 10 patients had values above 35 per cent. The highest value was 53 per cent in a 68-year old man who had moderate emphysema on pathologic section. It is again concluded that this ratio has poor discriminatory rating in early emphysema.

One of the striking findings in the present study is the relatively large number of 57 emphysematous patients in the total group of 150 tuberculous patients. A similar high proportion of emphysema was also reported in our previous communication.[9] Bell [17] found emphysema in a high percentage of rabbits chronically infected with human tubercle bacilli. If all patients with pulmonary tuberculosis may be assumed to be potential candidates for emphysema then it is permissable to review our young nonemphysematous group for the earliest sign of emphysema. Considering abnormalities in the three screening tests, elevation of the MBC spirogram seems to occur most often. The infrequent occurrence of prolonged TVC in the young age group and the widely scattered values in the older patients makes this a less valuable sign of early emphysema. The positive single breath test appears at a later age but an abnormal test is highly discriminatory at all ages.

An attempt to classify emphysema into stages would appear to be worthwhile in order to elucidate the progression of this disease as revealed by pulmonary function tests. The earliest sign may be the elevation of the MBC spirogram to the hyperinflation level persisting after maximum improvement is attained under treatment especially with bronchial dilators. Under conditions of maximum improvement, early emphysema may be suspected with reasonable certainty when the three screening tests mentioned above become positive. Based on these tests 39 patients had early emphysema. Moderately advanced emphysema is present when in addition to the positive ventilatory tests, the SB is 4 per cent or greater and the ratio of the residual volume/lung capacity x 100 is greater than 35 per cent in the young and 50 per cent in those over 50 years of age. At this stage the MBC is usually reduced below 70 per cent. Ten of our emphysematous patients fell into this group. Far advanced emphysema may be considered when the three screening tests are grossly abnormal, the MBC is in the range of 45 per cent or less, and the ratio of residual volume/total lung capacity is over 50 per cent. In the later stages the diffusing capacity becomes reduced, arterial O_2 unsaturation occurs, pulmonary artery pressure rises above normal first after exercise and later may be permanently elevated. CO_2 retention and respiratory acidosis complete the picture of pulmonary decompensation. Death occurs from intercurrent pulmonary infection, respiratory insufficiency, cor pulmonale, or spontaneous pneumothorax.

SUMMARY

One hundred and fifty tuberculous patients received pulmonary ventilatory tests prior to lobectomy for removal of residual disease or cavity. Patients were selected whose removed specimen yielded an "ideal biopsy" of the lung. The presence or absence of chronic obstructive emphysema was determined on the basis of gross inspection of the cut lung. The most sensitive indication of early emphysema was a combination of positive findings on all three ventilatory tests, TVC of 90 per cent or less, elevation of the MBC spirogram to hyperinflation level and single breath O_2 test of 2 per cent or greater. It was possible to predict correctly whether or not generalized emphysema was present in 93 per cent of the patients examined. A follow-up study on 94 of these patients showed no significant reversibility of the three ventilatory screening tests within an average period of six months postoperative. Only six patients appeared to develop emphysema within the six months following lobectomy.

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RESUMEN

Se hicieron pruebas ventilatorias en 150 enfermos previamente a la realización de lobectomías para resecar enfermedad residual o cavidades. Se escogieron los enfermos cuyo espécimen rindió un reporte de una "biopsia ideal" del pulmón.

La presencia o ausencia de enfisema crónico obstructivo se determinó por la observación macroscópica del corte de pulmón. La indicación más fina de enfisema temprano fué la combinación de hallazgos positivos de las tres pruebas de ventilación: TVC (Capacidad Vital por Segundos), elevación del espirograma de la MBC (Capacidad Máxima Respiratoria-CMxR) al nivel de la hiperinflación y la prueba simple de la respiración del Oxigeno de 2 por ciento o mayor.

Fué posible predecir correctamente si había o no enfisema generalizado en 93 por ciento de los enfermos examinados.

Un seguimiento de 94 de estos enfermos no mostró reversibilidad de significación de las tres pruebas ventilatorias mencionadas dentro de un término de seis meses después de la operación. Sólo seis enfermos parecieron desarrollar enfisema dentro de seis meses después de la lobectomía.

RESUMÉ

150 malades atteints de tuberculose furent soumis aux tests ventilatoires avant lobectomie pour exérèse d'une lésion résiduelle ou d'une cavité. Les malades choisis furent ceux pour lesquels la pièce enlevée représentait une "biopsie idéale" du poumon. La présence ou l'absence d'emphysème obstructif chronique fut déterminée sur la base d'un examen macroscopique du poumon coupé. L'indication la plus sensible de l'existence d'emphysème précoce fut une association de constatations positives portant sur les trois tests ventilatoires: test de la capacité vitale à 90% ou moins, élévation de la ventilation maximale à un niveau hyperélevé et test de la simple respiration oxygénée de 2% ou plus. Il fut possible de prévoir correctement s'il exis tait ou non un emphysème généralisé dans 93% des malades examinés. Un contrôle sur 94 de ces malades ne montra aucune réversibilité marquée des trois tests ventilatoires pendant une période moyenne de six mois après l'opération. Six malades seulement semblèrent développer un emphysème pendant les six mois qui suivirent la lobectomie.

ZUSAMMENFASSUNG

Es wurden 150 tuberkulöse Kranke Lungenfunktionsprüfungen unterzogen, ehe eine Lobektomie zur Beseitigung restlicher oder cavitärer Affektionen erfolgte. Patienten wurden ausgesucht, deren Operationspräparate eine "ideale Biopsie" der Lunge gestatteten. Das Vorhandensein oder Fehlen eines chronischen Obstruktions-Emphysems wurde auf der Basis der makroskopischen Inspektion der durchschnittenen Lunge bestimmt. Das empfindlichste Zeichen für ein beginnendes Emphysem bestand in einer Kombination positiver Befunde bei allen drei Lungenfunktionsproben: Sekunden-Vital-Kapazität von 90% oder weniger, Anstieg des Atemgrenzwert-Spirogramms und Sauerstoff-Atemstoß-Test von 2% oder mehr. Es war möglich, bei 93% der untersuchten Kranken genau im voraus zu bestimmen, oß ein generalisiertes Emphysem vorlag oder nicht. Eine Nachuntersuchung bei 94 dieser Kranken zeigte keine ins Gewicht fallende Umkehr der drei ventilatorischen Funktionsproben innerhalb eines durchschnittlichen Zeitabschnittes von 6 Monaten nach der Operation. Nur bei 6 Kranken schien sich im Verlaufe eines halben Jahres nach der Lobektomie ein Emphysem zu entwickeln.

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X-Ray Diagnosis of Radiation Injuries of the Lung

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The lung tissue, exposed to x-rays of sufficient intensity, eventually show signs, like other tissues, of damage, recognizable by inflammation and subsequently by scarring. Such damage has been known since 1922 and a number of papers testify to the clinical and pathological findings associated with irradiation. Engelstad and Warren and Spencer confirm these fiindings in histological and experimental investigations.

Rather different is the appreciation of the roentgenological picture in cases of radiation injuries of the lung. Observations of 50 cases with lung injuries following postoperative x-ray treatment for carcinoma of breast, led us to the definition of a pathognomic roentgen syndrome, useful in the diagnosis of pulmonary lesions following x-ray treatment for cancer of the breast.

Report of Cases

Case 1: R. R., woman, aged 44, June 1955: first examination at our chest clinic. From her history: carcinoma of the breast was operated on (about six weeks before) and treated by irradiation. The x-ray film shows evidence of slight fibrosis in the upper part of the right lung.—October, 1955: A large shadow with multiple bright spots were seen in the upper lobe of the right lung with shrinking of the whole right lung (Fig. 1.). Clinical symptoms consisted of general lassitude, cough, sputum, and pains in the right side of the chest. The erythrocyte sedimentation rate was 34 mm. in one hour. May 1956: porgressive scarring of the lesion in the right upper lobe was evident on anterioposterior Tomography studies the 9 cm; layer: the dense shadow contained numerous sharply defined hole-like bright spots of different sizes (Fig. 2.).—Meticorten brought no change in the roentgenological picture and did not improve the clinical condition.—In November, 1958, the latest follow-up examination revealed no change.

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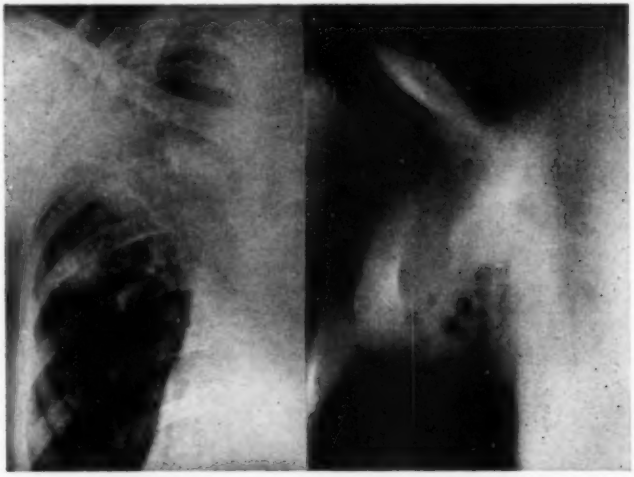

FIGURE 1 FIGURE 2

FIGURE 1: Large shadow with multiple bright spots in the right upper lobe. Shrinking of the whole right lung. FIGURE 2: Tomography A.P., layer 9: The dense shadow contains numerous sharply defined hole-like bright spots of different sizes.

Comment: This patient with radiation injuries suffered from severe clinical symptoms. According to the x-ray films, the lesion apparently was irreversible. Tomographic analysis revealed the characteristic signs of radiation fibrosis: enlargement of the medium-sized and small bronchi, depicted as hole-like clear spots in the sclerotic tissue with their localization exclusively in the anterior layers of the infraclavicular zone.

Case 2: S. M., woman, aged 55. In October, 1956 the left breast was resected because of carcinoma. This was followed by x-ray irradiation. In March, 1957, the x-ray film did not show pathological findings. In May, 1957, there was evidence of fibrosis in the right upper lobe and signs of bronchiectasis (Fig. 3). She had fever and cough. The erythrocyte sedimentation rate was 48 mm. in one hour. At the 5 centimeter level posterioranterior tomography revealed enlarged bronchi surrounded by sclerotic lung tissue (Fig. 4). April, 1958: considerable resorption of the fibrosis apparently had occurred and she feels well.

Comment

The classical picture of radiation injuries is seen clearly on tomography in its anterior layers with bronchiectasis in the fibrotic tissue. In the course of our observation over a long period, the reversibility of the damage could be demonstrated.

Discussion

Cases of carcinoma of the breast seemed to us most instructive for studying radiation injuries of the lung, as they usually undergo x-ray treatment after the operation, and, as there are no pathological signs in the lung previous to radiation, the changes noticed afterwards are most likely caused by the treatment. Clinical and roentgenological examination form the basis of our conclusions. There are no autopsy findings at our disposal, nor was it possible to assess statistically the exact incidence of radiation injuries in the lung. Engelstad and Chu believed that 5.4 per cent of all treated persons suffered from radiation damage. On the other hand, Ross and MacIntosh think, the frequency amounts to 60 per cent.

Our cases were women aged from 32 to 71. Only five were younger than 40 (Table 1.). Relatively young patients suffered eventually the most severe injurjes. In 20 of our 50 cases, (40 per cent,) the injuries manifested themselves only in the radiological findings and did not produce clinical symptoms (Table 1.). Where symptoms occurred, the most outstanding were: dyspnea (13 cases), cough and sputum (11) and chest pain (6). A long period of observation is the essential condition for any conclusion to be drawn about the final outcome of radiation injury to the lung. Our observation extended in 39 cases for more than two years (Table 1), in 18 cases for more than three years, and only in 11 cases the period of observation was one year.

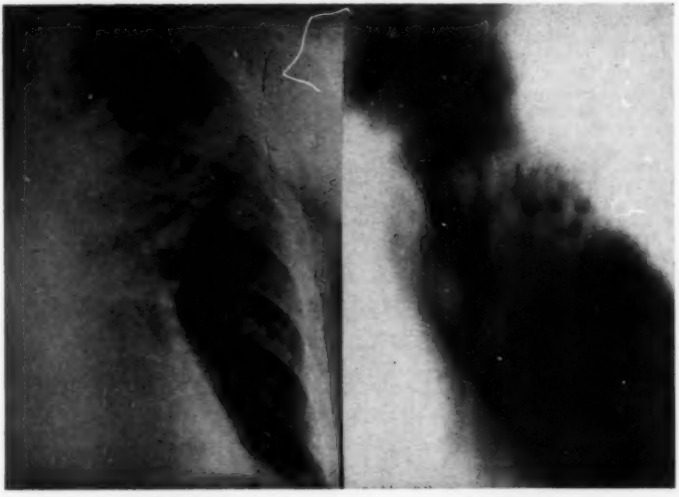

FIGURE 3 FIGURE 4

FIGURE 3: Fibrosis in the right upper lobe and signs of bronchiectasis. FIGURE 4: Tomography P.A., layer 5: Enlarged bronchi surrounded by sclerotic lung tissue.

TABLE 1 — RADIATION INJURIES OF THE LUNG

Age	Clinical Symptoms	Period of Observation	Localization
32 - 71 years	13 cases: Dyspnea	11 cases: 1 year	44 cases: infraclavicular
	11 cases: Cough, Sputum	21 cases: 2 years	
(5 cases below 40 years)	6 cases: Pains	11 cases: 3 years	6 cases: the whole hemithorax
	20 cases: Symptom free	7 cases: more than 3 years	

Pathological-anatomical investigations make it clear, that there are two stages in the process of radiation damage. Our roentgenological examinations confirm these two stages. The early reaction has an exudative character, the so-called radiation pneumonitis, which is followed by the radiation fibrosis, representing the second stage. Each one is clearly reflected in the radiological picture. At the beginning, during the acute inflammation, a homogenous shadow is to be seen in the irradiated area, mostly in the infraclavicular part of the lung. This was found in 44 of our 50 cases (Table 1). In the fibrotic stage, the x-ray films show ribbon-like shadows, clearly defined, connecting the hilus and the periphery of the lung. Radiation injuries are never seen in the roentgen picture until at least one month after the irradiation. They may take a variable course and are not subject to any rule. Occasionally, a rapid complete resorption takes place; in other cases, a transformation in the fibrotic phase. Even this fibrotic stage may show almost full resolution after a period of prolonged observation.

In the differential diagnosis, two important points have to be stressed: 1) the localization of the lesions is in the anterior layers, which are the most exposed to x-rays during the irradiation. This is particularly important in the differential diagnosis from tuberculosis; 2) there is a peculiar pattern in the tomographic picture: dense shadows are seen with numerous hole-like bright spots, representing the enlargement of numerous medium-sized and small bronchi. This finding, outlined in the anterior layers, seems to be pathognomic of radiation injuries of the lung following x-ray treatment of carcinoma of mammae. In the following, a classification of our 50 cases is given in relation to the severity of radiation damage (Table 2): 1) slight injuries, roentgenologically noticed as ribbon-like shadows in the radiated area; 2) severe injuries — extensive scars and bronchiectasis, with destruction of the lung tissue; 3) moderately severe injuries, which are of greater extent and intensity than in group 1, but not as advanced as in group 2. In this series, the cases with severe injuries were in the majority (27), while slight damage was found in only six cases. The above classification was applied in order to assess and compare the clinical with the roentgenological manifestation and severity of the disease. As already mentioned, 20 patients had no clinical symptoms, i. e. 40 per cent of the total number of 50. But by taking only the severe cases into account, the proportion of symptom free patients was 18 per cent (five cases). All but one of the 13 patients who suffered from severe dyspnoea belonged to this group (Table 2). From the slightly injured, only one patient complained about pains in the operated side of the thorax. The conclusion may be drawn that on the whole there exists a parallelity between the severity of the damage, as seen roentgenologically and the clinical symptoms, but the correlation can not be exactly defined. The observation of the 27 severe cases enabled us to follow the course of the process of radiation injuries and to draw some conclusions about the final result: Radiologically 16 cases did not show signs of resorption, and a heavily scarred tissue took the place of the primary lesion. In 11 cases, the damage appeared at first to be irreversible, but during further observation the signs of resorption became quite remarkable. For the treatment of radiation injuries of the lung tissue, cortisone has been advocated. We administered it in six cases of severe pneumonitis, but the x-ray did not show changes resulting from this therapy. The publications in the literature report similar results. There may be cases where resection of the affected part of the lung is indicated (Bergmann, Graham).

TABLE 2 — SEVERITY OF INJURY AND CLINICAL SYMPTOMS

Slight:	6 cases	1 case: Pains	
		5 cases: Symptom free	
Moderate:	17 cases	1 case: Dyspnea	
		5 cases: Cough	
		1 case: Pains	
		10 cases: Symptom free	
Severe:	27 cases	12 cases: Dyspnea	Final status
		7 cases: Cough and Sputum	11 cases: reversible
		3 cases: Pains	16 cases: irreversible
		5 cases: Symptom free	

SUMMARY

A report is presented of 50 cases with radiation injuries of the lung tissue due to post-operative x-ray treatment for carcinoma of the breast. Thorough roentgenological and clinical examinations have been the basis in this investigation. Tomographical studies lead to the conclusion that radiation injuries of the lung tissue manifest themselves in characteristic fibrotic changes with dilatation of numerous medium-sized and small bronchi in the anterior layers of the lung. The picture reflects the pathological process and when combined with history of radiation is considered pathognomic.

RESUMEN

Se relatan 50 casos con daño por radiación consecutivo a tratamiento con rayos X por carcinoma mamario. Las bases de esta investigación han sido los exámenes clínicos y radiológicos completos.

Los estudios tomográficos condujeron a la conclusión de que la lesión por radiación del pulmón se manifesta de modo característico: fibrosis con dilatación de numerosos bronquios de mediano calibre en las capas anteriores del pulmón. El aspecto refleja el proceso patológico que cuando se combina con antecedentes de radiación, es patognomónico.

RESUMÉ

L'auteur présente une communication de 50 cas atteints de lésions par irradiations du tissu pulmonaire, consécutives à un traitement radiologique post-opératoire pour cancer du thorax. Cette étude est basée sur des examens radiologiques et cliniques complets. Les tomographies ont permis de conclure que les lésions par irradiation du tissue pulmonaire se manifestent par des altérations fibreuses caractéristiques avec dilatation de nombreuses bronches de moyen et petit calibre dans les parties antérieures du poumon. L'image montre bien le processus pathologique et quand il s'associe à la notion d'irradiation antérieure, il peut être considéré comme pathognomonique.

ZUSAMMENFASSUNG

Es handelt sich um einen Bericht über 50 Fälle von Strahlenschädigung des Lungengewebes in Zusammenhang mit postoperativer Röntgentherapie wegen Mammacarzinom. Umfassende rontgenologische und klinische Untersuchungen bildeten die Grundlage dieser Analyse. Tomografische Studien führten zu dem Schluß, daß sich Strahlenschädigungen des Lungengewebes in charakteristischen fibrotischen Veränderungen manifestieren mit Dilatation zahlreicher mittelgroßer und kleiner Bronchien in den ventralen Schichten der Lunge. Dieses Bild ist der Spiegel des pathologisch-anatomischen Prozesses und kann in Verbindung mit einer Vorgeschichte von Bestrahlung als pathognomonisch angesehen werden.

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An Analytical Review of Extra-Periosteal Plombage Thoracoplasty

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Introduction

The purpose of this paper is to record our experience with extra-periosteal plombage thoracoplasty, as done in our hospital from 1953 to 1958. Although the period is not sufficiently long to justify the proper evaluation, nevertheless, an attempt has been made to discuss the results of our series of 135 cases in their various aspects to compare our findings with series published by other authors.

Thoracoplasty has been accepted as one of the most effective procedures in the surgical treatment of pulmonary tuberculosis during last 50 years. In spite of many arguments against it, and new procedures like resections with their flattering statistics catching the imagination of the surgeons there are workers who still believe in the efficacy of this age-old procedure as devised by Alaxender. The arguments in favor of thoracoplasty lie in the fact that it aims at achieving physiological conditions which the human body tends to achieve, when attempting to arrest tuberculosis. It permits collapse of diseased area, enabling the fibrotic healing process to contract the destroyed lung parenchyma, leaving the rich blood supply of chest wall in contact with the lung.

Because of the traumatic nature of thoracoplasty and the subsequent deformity induced by it and also because of the sacrifice of a portion of the healthy pulmonary tissue involved in the technique of the operation, attempts have been made to devise procedures which could replace thoracoplasty in suitable cases. The pulmonary and segmental resections have almost succeeded in replacing thoracoplasty in an effective manner. At a time when new methods are introduced and old are being abandoned, it is our hope that this paper will help in the proper assessment of the value of plombage thoracoplasty, in suitable cases.

Historical

Extrapleural pneumolysis was used periodically at the close of the last century. Tuffer in 1911 performed the first space filling with patients body fat; Baer in 1913 used sterilized semi-solid paraffin; Archibald in 1921 used the pedicle of pectoral muscle; Ougherteson and Harvey in 1931 used inflated rubber bag and Wilson introduced lucite spheres in 1948.

Our Plombage Material

In 90 per cent of our series, we used commercially available ping-pong balls as space filling material, as they satisfied all the requirements of a good plombage material: visibly — light, easy-sterilizability, non-antigenic and non-irritating properties. Besides, they have been easily available and extremely cheap.

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The quantity of plombage material used by us for filling the space was just enough, which would snugly fill up the extra-periosteal space, without exerting much pressure on the shelf.

Operative Technique

All our patients were operated under local anesthesia after infiltration of 1 per cent Novocaine solution. Operation was performed in the lateral prone position usually employed for a conventional thoracoplasty. Sufficient care was taken not to denude the ribs completely in order to maintain the nutrition and blood supply to the ribs by keeping the superior periosteum intact. The first rib is not cleaned on the upper surface in order to prevent the escape of the spheres into the neck.

On the third postoperative day, the patients were aspirated and 5 lacs units of crystaline penicillin and 1 gm. of streptomycin dissolved in 10 cc. of normal saline were instilled into the space. On an average, no more than two or three aspirations have been necessary. The patients were kept under the screen of anti-biotics, Isonex and PAS daily for a period of two weeks. Stitches were removed on the 10th day.

Our Case Series

In March, 1953, we performed our first extra-periosteal ball plombage in a relatively poor risk case. The result of subsequent cases where other surgical measures would have been risky were very encouraging. This gave us an impetus to widen the indications as a result of which we employed this measure on 135 cases in all age groups as well as in all stages of the disease. This procedure was also employed in two patients complicated by diabetes and also in two pregnant women running the fifth month.

Age: Age of the patients included in the series ranged from 18 to 68 years. Only one patient was below 20 years and two above 60 years. Forty-seven per cent of patients belong to age group between 30 to 40 years and 34 per cent belong to age group of 20 to 30 years.

TABLE SHOWING AGE GROUPS

Age	*Number of Patients*
10 to 19	1
20 to 29	46
30 to 39	63
40 to 49	8
50 to 59	15
Over 60	2
Total	135

Sex: Out of 135 cases, 93 (70 per cent) were men and 42 (30 per cent) were women.

Extent of Disease: Ninety-eight patients (73 per cent) showed a "far advanced disease" where resection was not possible and plasty was a poor risk and 27 per cent belonged to "moderately advanced" group.

Sputum Status: Ninety-three per cent of the patients in the series were sputum positive by direct smear method, while 7 per cent were negative,

TABLE SHOWING EXTENT OF DISEASE

Type	*Number*	*Per cent*
Minimal	Nil	0
Moderate	37	27
Far Advanced	98	73

TABLE SHOWING DURATION OF DISEASE AND SIZE OF CAVITY

Duration of Disease		Size of Cavity	
Period	*No. of patients*	*Diameter in cms.*	*No. of patients*
Less than 6 months	41		
6 months to 1 year	37	More than 4 cms.	98
1 year to 2 years	37	Less than 4 cms.	37
Over 2 years	20		
TOTAL	135	TOTAL	135

though all of them had definite radiological evidence of cavitation and previous history of positive sputum.

Contralateral Disease: Fifty-eight per cent of the patients from the series had a well established disease in the opposite lung, which was stabilized or comparatively inactive at the time of the operation.

Previous Treatment: Most of the patients in the series received antibiotics and chemotherapeuticals ranging for a period of one month to twelve months prior to operation.

Eighty-eight patients (60 per cent of the total number) had undergone previous collapse measures such as pneumoperitoneum, pneumothorax. Twenty per cent of the total had a phrenic crush.

TABLE SHOWING DURATION OF ANTI-MICROBIAL TREATMENT BEFORE SURGERY

Under 1 month	4
1 to 6 months	37
6 months to 1 year	74
Over 1 year	20
TOTAL	135

TABLE SHOWING COLLAPSE MEASURES RECEIVED BY 135 PATIENTS BEFORE OPERATION

Collapse measure	*No. of patients*
Artificial Pneumothorax	1
Pneumoperitoneum	88
Phrenic Crush	27
No collapse therapy	19
TOTAL	135

Complications

Massive fluid formation (reactionary) and subsequent pressure symptoms with dyspnea was observed in two cases which required immediate aspiration. The rest of the post operative course was uneventful and the patients recouped without any further complications.

Two patients showed increase in the pre-existing contralateral disease which cleared later on, after treating them by artificial pneumoperitoneum and chemotherapy.

Tuberculosis infection of the extra-periosteal space developed in three cases with high rise in temperature and palpable fluid accumulated beneath the scar tissue. The pus was drained and the plombs, i.e. balls, were removed and conventional thoracoplasty was done in all the cases. The patients recouped without any further complications.

Non-specific infection of space occurred in two cases which cleared on massive dosage of broad spectrum therapy.

Asceptic osteolysis of ruginated ribs occurred in three cases after six months' post operative period.

Three deaths occurred; two due to coronary thrombosis and one accounted by nephritis during the post operative period.

Follow up of Operated Cases

Most of the cases have been reporting to us for regular check up every two months, which has made the follow up for a period of five years possible. We have been in a position to follow up 126 patients for a period of five years. Out of this number, 70 patients have been arrested cases which have shown repeated negative stomach washes and show a normal arrest of the disease in the x-rays for a period of five years. Most of these cases have been rehabilitated to normal active life. The remaining 56 cases are still in a much improved condition, i.e., clinically they feel fit. Their repeated x-rays show no evidence of active lesions, but their sputum status varies from time to time from negative to positive and positive to negative.

Discussion

The operation of extra-periosteal pingpong ball plombage has proved to be a simple and safe procedure, apparently a good and reliable substitute for multi-stage thoracoplasty, particularly in cases where the latter is considered to be a great risk.

This procedure has definite advantages over the conventional thoracoplasty which are enumerated below:

(1) Lack of shock even in extensive cases where extensive stripping of 7-8 ribs has been done.

(2) The collapse is created in a single surgical procedure.

(3) The sputum conversion is much quicker; in many cases we have found it to be negative during the very first month after the operation.

(4) Paradoxical movements are insignificant and negligible. As a result, there is less interference with respiration and there is less cough.

(5) The degree of deformity and skoliosis is negligible, as the first rib is kept intact. The functional loss is less as compared to conventional plasty or resection.

(6) The collapse failures can be treated by a conventional thoracoplasty or resections.

(7) It is much more safe than the resection method in patients harboring resistant acid-fast bacilli.

(8) Above all, it is the simplest and safest procedure of all major surgical collapse methods or resections.

The most suitable cases for plombage thoracoplasty are persistent cavities under 4 cms. in diameter in the apical or posterior segments of upper lobes. It is definitely indicated in poor surgical risk cases, old age and also extensive bilateral cases where other procedures can not be undertaken.

One of the problems which would be answered in course of time is the problem of safety of leaving the plombage material in space, in order to avoid the second operation. Our experience so far indicates that the plombage material, particularly ping-pong balls, are well tolerated by most of the patients for a period of well over four years so far.

SUMMARY

Extra-periosteal plombage remains still a procedure of choice in cases where other surgical measures cannot be easily employed. It is particularly indicated in old patients and cases with extensive disease.

Our experience so far with 55 per cent of cases arrested out of a total of 135 patients for a period of over five years is very encouraging, in view of the fact that it was adopted only in patients who showed an extensive disease and who were a poor risk group.

RESUMEN

El plombaje extrapleural es aún un procedimiento de elección para los casos en que no pueden usarse otros procedimientos. En particular está indicado en los ancianos y en los casos con enfermedad muy extensa. Hastan ahora nuestra experiencia con 55 por ciento de casos detenidos más de cinco años es muy alentadora, en virtud de que adoptamos el procedimiento sólo en los casos con demasiada extensa enfermedad o que constituían riesgos muy graves.

RESUMÉ

Le plombage extra périosté reste encore un procédé de choix dans les cas où les autres moyens chirurgicaux ne peuvent être facilment utilisés. Il est particulièrement indiqué chez les malades âgés et dans les cas d'affection extensive. Notre expérience qui nous apporte 55% de malades stabilisés sur un total de 135 pour une période de plus de cinq ans est très encourageante, surtout si l'on considère que se procédé ne fut adopté que chez les malades qui étraient atteints d'une affection extensive et qui appartenaient à un groupe comportant beaucoup de risques opératoires.

ZUSAMMENFASSUNG

Die extraperiostale Plombierung bleibt auch heute noch das Verfahren der Wahl für Fälle, in denen andere chirurgische Maßnahmen nicht ohne weiteres zur Anwendung gelangen können. Sie ist im besonderen angezeigt bei älteren Patienten und Fällen mit ausgedehnten Befunden.

Unsere bisherigen Erfahrungen mit 55% zum Stillstand gekommenen Fällen bei einer Gesamtzahl von 135 Kranken in einem Zeitraum von mehr als 5 Jahren sind sehr ermutigend im Hinblick auf die Tatsache, daß die Plombierung nur bei solchen Kranken erfolgte, die einen ausgedehnten Befund aufwiesen und die Gruppe der schlechten Risiken umfaßte.

Prolonged Use of Oxytetracycline Hydrochloride with Glucosamine in Twenty-five Patients for Nonspecific Complications Associated with Pulmonary Tuberculosis

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During a previous study[1] we had used oxytetracycline in conjunction with other antituberculosis drugs for the treatment of tuberculous infection. This study proved that oxytetracycline may be employed to great advantage as an ancillary drug along with isoniazid, streptomycin or viomycin. While using oxytetracycline in this way, and over a considerable period of time, we were impressed with its apparent lack of toxicity and also with an apparent reduction in secondary nonspecific complications such as sinus infections, bronchial conditions and the like.

Based on this experience, we decided to administer oxytetracycline in the amount of 1,000 milligrams per day, in divided doses of 250 milligrams four times a day, to a group of patients who had been plagued by such secondary nonspecific infections during the past. This adjunctive therapy was employed with no regard to the basic antituberculosis medication, and not in an effort to replace one of the antituberculosis drugs in use. In this way, oxytetracycline was added to the routine antituberculosis drug therapy in a group of 25 patients. Of these, five had to be discontinued either on account of gastro-intestinal irritation or simply having refused to accept it. The remaining 20 patients have received the above outlined medication for a period of four to six months without interruption. All of these cases have active advanced pulmonary tuberculosis and all receive routine combinations of antituberculosis drugs. Eleven are on streptomycin and isoniazid in the usual dosage; the others receive combinations of streptomycin and PAS, or INH and PAS.

The reasons for adding oxytetracycline to the antituberculosis medication in these 20 patients were: twelve had previously suffered from frequent colds and recurrent attacks of bronchitis with elevation of temperature; four had severe bronchiectasis as cause for their recurrent secondary infections, and two had chronic recurrent sinusitis. Two others had recurrent genito-urinary infections of a nontuberculous nature.

Reviewing the results of the addition of oxytetracycline to the basic antituberculosis medication in these cases, we were impressed by a considerable, almost dramatic, reduction in toxicity, and by the decrease of secondary infections and fever in most of them. As a matter of fact, the group treated with oxytetracycline fared better through the winter than those who had no known prior secondary infections and who did not receive this additional drug. Evaluating the result from a clinical point of view, the effect on secondary infections, fever, and general improvement, has been excellent in 12 of the 20 cases, and satisfactory

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in another seven. No apparent result was seen in one case, in which an unexpected breakdown of the tuberculous infection occurred with cavity formation, and this despite the intensive antituberculosis medication plus the addition of oxytetracycline.

Encouraged by the result of prolonged adjunctive use of oxytetracycline in these 20 cases, we used the same drug routinely in another 10 of our patients for simple intercurring infections or febrile attacks of unknown origin as adjunctive therapy in addition to the regular antituberculosis medication. Tentative diagnoses in these 10 cases were: severe colds in five, kidney infection in one, diverticulitis in two, and postsurgical treatment for empyema in another two. In most of them, improvement and recovery from the secondary infections was rapid and uneventful and therapy was discontinued after a period of from three days to two weeks.

Reviewing all these cases, we are again impressed by the almost complete lack of toxicity. Except for a few cases who either cannot or do not think they can tolerate the drug as far as their gastro-intestinal tract is concerned, we have found no toxic by-effects except for one case of vaginal moniliasis in a woman which may have been related to the use of the antibiotic. Urinalysis and blood counts were done routinely every month and there was no toxic effect on either one. Sensitivity studies were not carried out, but from a clinical point of view there was no reduction in the effectiveness of the oxytetracycline even after prolonged use, and no apparent intolerance developed in any of these cases.

SUMMARY

The beneficial effect of 1,000 milligrams per day of oxytetracycline along with the regular antituberculosis drugs in cases of pulmonary tuberculosis complicated by secondary infections such as sinusitis, bronchitis, frequent upper respiratory infections or secondary infections of other nature has been demonstrated.

RESUMEN

Se han demostrado los efectos benéficos de 1,000 miligramos por día de oxitetraciclina, unida a las drogas antituberculosas en caso de cirugía de la tuberculosis complicada con infecciones secundarias o infecciones de vías respiratorias altas.

RESUMÉ

L'auteur a montré l'effet bénéfique de 1.000 mmg. par jour d'oxytétracycline associé aux produits antituberculeux habituels dans les cas de tuberculose pulmonaire compliquée d'infections secondaires telles que sinusite, bronchite, infections fréquentes des voies respiratoires supérieures, ou infections secondaires d'autre nature.

ZUSAMMENFASSUNG

Beschreibung der heilsamen Wirkung von 1,000 Milligramm täglich Oxytetracyklin zusammen mit den übrigen Tuberkuloseheilmitteln bei solchen Fällen von Lungentuberkulose, die durch Sekundärinfektionen sowie Sinusitis, Bronchitis, häufige Infektionen der oberen Luftwege oder Sekundärinfektionen anderer Natur kompliziert waren.

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SECTION ON CARDIOVASCULAR DISEASES

An Electrocardiographic and Autopsy Study of Coronary Heart Disease in the Navajo*,**

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Case records of and autopsies on Navajo Indians and a white control group were reviewed and compared in a study designed to determine differences in the prevalence of coronary heart disease which are said to exist between the two groups. Navajo autopsies had not been reviewed in previous reports. The autopsy and clinical data seem to confirm the existence of a low prevalence of coronary heart disease in the Navajo.

This is a preliminary report of a continuing study of coronary heart disease in the Navajo.

Indian Service and Public Health Service physicians as well as medical missionaries working in the Navajo country of Arizona and New Mexico have noted repeatedly a near absence of admissions of Navajo patients who were experiencing, or who had experienced, symptoms suggesting coronary artery disease. Gilbert[1] reviewed the diagnoses at the Navajo Medical Center over a five-year period and found only five Navajo patients in whom a diagnosis of coronary heart disease had been made. Smith[2] examined the death certificates of Navajos, extending the analyses of a previous study and comparing expected mortality with recorded mortality, making corrections for possibilities of faulty certification. He found that the cardiovascular-renal diseases, with the exception of rheumatic fever, were less frequently encountered among the Navajos than in the general white and non-white populations of the United States. Keys,[3] however, found that coronary heart disease was not "vanishingly rare" among the Navajos. His conclusion was based upon a study of diagnoses in the Navajo Medical Center hospital during the year 1955-56. Of a total of 115 men admitted to the medical division of the hospital, there were eight recorded diagnoses of arterio-sclerotic heart disease and two of myocardial infarct.

The present report is the result of an investigation designed to determine the frequency of coronary heart disease in patients admitted to the Navajo Medical Center Hospital as determined by autopsy and electrocardiographic data compared with those from a control group of white patients. It was felt that, if the material from Gilbert and Smith were

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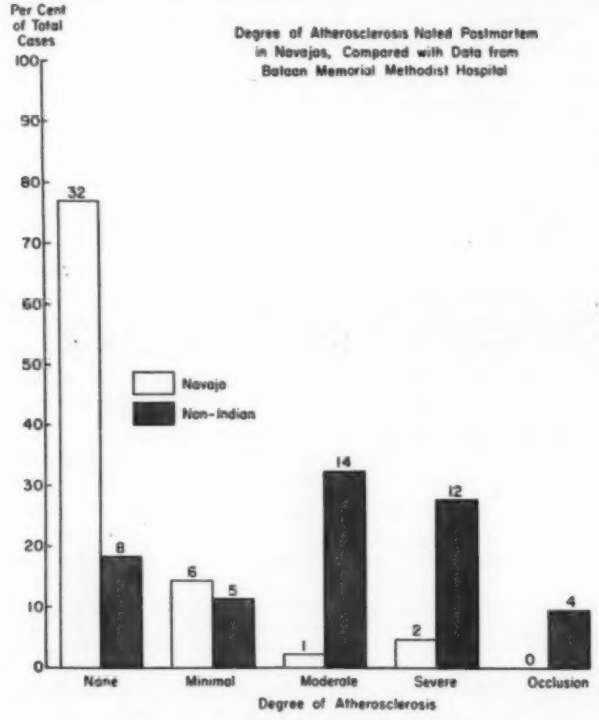
correct, it would be of considerable importance to pursue a sound epidemiological study within the Navajo tribe in order to assess more accurately the prevalence of this disease entity and to evaluate factors which might have some bearing upon the apparent differences in incidence between the Navajo and the white population. There seemed to be the possibility that a greater prevalence of coronary heart disease existed in the Navajo than had been previously suggested.

Method

Clinical Data

The records of all patients over the age of 30 who had had electrocardiographic studies made during their hospitalization were reviewed. There were 4,741 admissions of Navajo Indians 31 years of age or older during the period July 1, 1950, through September, 1956, and 324 of them were found to have had electrocardiograms made. Indians of tribes other than the Navajo were excluded from the study. The records of the 4,416 patients who did not have electrocardiograms were not reviewed. Of the records reviewed, 11.6 per cent consisted of Leads I, II, and III only and 0.2 per cent consisted of Leads I, II, III, and IVF. The remaining 88.2 per cent consisted of the conventional 12-lead electrocardiograms.

As a control, the charts of white patients who had had electrocardiographic studies during their hospitalization at Bataan Memorial Methodist Hospital in Albuquerque were reviewed. Of 1,478 consecutive ad-



missions of patients 31 years of age or older, during the period of September 1, 1957 to February 28, 1958, there were 364 records acceptable for review on this basis. The records of the 1,114 patients who did not have electrocardiograms during their admission were not reviewed. All of the 364 patients had 13-lead electrocardiograms.

The electrocardiograms were classified according to generally accepted diagnostic criteria. They were classified as follows:

Definite acute or old myocardial infarction — Definite ECG evidence of myocardial infarction.

Probable acute or old myocardial infarction — Definite clinical or historical evidence with very suggestive ECG changes.

Inconclusive — Non-specific ST-T changes or Bundle branch block (Suggestive ECG changes but complicating factors involved; e.g., hypertension, valvular heart disease, metabolic changes, drugs).

Normal

Autopsy Data

The autopsy data were derived from material from three institutions: the Navajo Medical Center in Fort Defiance, Arizona, the Bataan Memorial Methodist Hospital and the Bernalillo County-Indian Hospital, both in Albuquerque, New Mexico. With one exception, only those cases 31 years of age or older were included in the analysis. A 28 year-old Navajo who died during an alcoholic stupor was included because he was found to have moderately severe atherosclerotic changes in his coronary arteries.

There were 45 autopsies on Navajo patients available for study and 43 autopsies on white patients.

The 11 autopsies at the Navajo Medical Center were performed by the medical officer in attendance, with histologic study completed by the pathologists at the Lovelace Clinic or by pathologists at the National Institutes of Health, Bethesda, Maryland. Postmortem examinations done at Bernalillo County-Indian Hospital and at Bataan Memorial Methodist Hospital were performed by the pathologists at the institutions.

TABLE 1 — PATIENTS HAVING HAD ECG STUDIES
NAVAJO MEDICAL CENTER AND BATAAN MEMORIAL METHODIST HOSPITAL

	NMC		BMMH	
ECG Findings	No. Cases	Per cent	No. Cases	Per cent
Definite Acute	3	0.9	30	9.2
Definite Old	6	1.8	12	3.5
Probable Acute	3	0.9	6	1.7
Probable Old	7	2.1	11	3.3
Inconclusive	26	8.2	102	26.6
Normal	279	86.1	203	55.7
Total	324	100.0	364	100.0
Mean Age	60 years		57 years	
Men	170	55.9	178	48.9
Women	154	44.1	186	51.1

As a control, all autopsies performed on white patients 31 years of age or older at the Bataan Hospital during 1956 were reviewed in the same manner.

The statistics given represent the pathologist's or prosector's opinion regarding the degrees of atherosclerotic involvement of the coronary arteries. In so far as this was possible, the following classification was utilized:

Slight — Occasional focal plaques with little or no encroachment upon the lumen.

Moderate to Marked — Up to 75 per cent narrowing of the lumen.

Severe — Greate rthan 75 per cent narrowing of the lumen.

Occlusion — Obliteration of the lumen.

In most of the Navajo group the lack of atherosclerotic change in the coronary arteries was associated with a similar lack of atherosclerotic change in the other large arteries examined.

Results

The electrocardiographic findings in both groups are summarized in Table 1. It is seen that the mean ages of the Navajo and white groups are comparable, being, respectively, 60 and 57 years.

There is a lower percentage of women in the Navajo group than in the white, the figures being 44.1 per cent and 51.1 per cent, respectively.

Normal tracings were encountered much more frequently in the Navajo group, 86.1 per cent of them having normal electrocardiograms compared with 55.7 per cent in the white.

The electrocardiographic diagnoses can be confidently related to the existence of myocardial infarction when the pattern is both characteristic and acute. It is in this group that the differences between the Navajo and white are most apparent. In the Navajo group, 0.9 per cent had characteristic acute myocardial patterns, while 9.2 per cent of the white group exhibited these changes. This difference is highly significant statistically. The figures for all definite myocardial infarction patterns, either acute or old, were 2.7 per cent for the Navajo and 12.7 per cent for the white. This is a significant difference, but it is of a lesser degree.

The differences between the Navajo and white groups are not significant when the electrocardiographic patterns are less characteristic of myocardial infarction. Thus, in the probable myocardial infarction cases

TABLE 2 — PATIENTS WITH ECG STUDIES COMPARED WITH TOTAL ADMISSIONS

	NMC		BMMH	
ECG Findings	No. Cases	Per cent of All Admissions	No. Cases	Per cent of All Admissions
Definite Acute	3	.063	30	2.03
Definite Old	6	.126	12	.81
Probable Acute	3	.063	6	.40
Probable Old	7	.147	11	.75
Inconclusive	26	.548	102	6.90
Total abnormal	45	.949	161	10.89

there are 3.0 per cent and 5.0 per cent in the Navajo and white groups, respectively. This difference could be explained by reference to the inherent error involved in the electrocardiographic diagnosis of coronary heart disease.

Significant as these figures seem to be, it should be pointed out that the number of cases in each category in the Navajo group is actually the number in 4741 admissions; whereas the number in each category in the white group is that number in 1478 admissions. In each group there were undoubtedly patients who did have coronary artery disease but who did not have an electrocardiographic study and who, therefore, would be missed in this type of study. Errors of this kind should exist with nearly equal frequency in both groups, although it might be argued that such errors of omission would be slightly greater in the Indian patients because of the difficulty in obtaining good histories.

Nevertheless, the diagnosis of acute myocardial infarction was made three times in 4,741 admissions of Navajo patients over 30 years of age as opposed to 30 times in 1,478 white patients in the same age group. This is a ratio of 1:32. Including all definite infarct patterns, these were seen nine times in 4,741 Navajo patients and 42 times in 1,478 white patients, giving a ratio of 1:15.

Expressed in percentages, 0.19 per cent of the Navajo patients showed patterns diagnostic of myocardial infarction, whereas 2.84 per cent of white patients showed similar patterns.

The ratio of abnormal electrocardiographic patterns in the Navajo to abnormal patterns in the white group was about 1:10, if we make the assumption that those patients who did *not* have electrocardiograms made were normal. Without this assumption, the ratio is still 1:3.

These comparison are shown clearly in Table 2.

The autopsy findings are summarized in Table 3 and are given in graphic form in the figure. The differences observed between the white group as represented by the Bataan Memorial Methodist Hospital cases and the Navajo group are highly significant. As may be observed from

TABLE 3 — AUTOPSY DATA

Degree of Atherosclerosis	Total Navajo	Per cent	BMMH	Per cent
None	32	78.2	8	18.6
Minimal	6	14.6	5	11.6
Moderate and Marked	1	2.4	14	32.6
Severe	2	4.8	12	27.9
Occlusion			4	9.3
Inadequate Protocol	3			
Other Tribe	1			
Totals	45		43	

P=>> 0.001 for the differences in data between white and Navajo.

	Navajo	White
Men	26	23
Female	19	20
Age Range	33-80	31-88
Mean Age	61	62

the table, 21.8 per cent of the Navajo patients over 31 years of age showed some degree of atherosclerosis. In the white group over 31 years of age the incidence of atherosclerosis was found to be 81.4 per cent.

Discussion

Based on the material obtained for this study, it would seem apparent that coronary heart disease does exist in the Navajo Indian in Southwestern United States, albeit its frequency is probably one-fourth to one-tenth that of this disease in the adult white population in this area. Further, there apparently is not an absence of coronary thrombosis as implied by Gilbert, because we encountered characteristic myocardial infarction patterns in the electrocardiograms of nine Navajo patients.

The incidence figures for both the Navajo and white groups in this study may be erroneous, since they are based upon that group of patients who had electrocardiograms made during hospitalization. The assumption is made that most patients showing symptoms suggestive of heart disease would be included in these groups, since the availability of electrocardiographic study is essentially the same at the Navajo Medical Center as at Bataan Memorial Methodist Hospital in Albuquerque. It might be advanced, however, that fewer Navajos would seek hospitalization for the symptoms of coronary disease than whites, particularly if these symptoms were not disabling. Physicians working with the Indians in this area recognize that cultural differences lead to differences in the patients' interpretation of chest pain and his judgment as to the gravity of this symptom.

Further, the white population studied is largely an urban group with ready access to hospitalization. Many Navajos live great distances from a hospital facility, distances which are further magnified by roads which may be poor at best, and impassable in wet weather. The so-called poor risk coronary patient who, in Albuquerque, would be brought to the hospital by ambulance, on the reservation might never start or complete his difficult journey to the hospital. This factor may be reflected in the greater difference seen between the white and Navajo groups in the number of cases showing characteristic changes of acute myocardial infarctions as compared with that group showing old ECG changes. Other studies have shown differences between urban and rural populations in this regard where the factor of racial difference is probably unimportant.

Despite these considerations, we were impressed that there does indeed exist a smaller incidence of coronary heart disease in the Navajo Indian than in the white in a similar age group. We have attempted to make no judgment regarding the reasons for this difference. A study is currently in progress by our group on the cholesterol levels and electrophoretically determined serum lipid fractions, but thus far involves too few cases to permit any generalizations. Reasonably accurate and comprehensive dietary studies had not been done until those of Darby et al.[5] These studies seem to suggest no real difference between the dietary patterns of the more prosperous Navajo and other omniverous peoples. The percentage of calories derived from fat is probably about the same in the diets of whites and prosperous Navajos; the source of the fat may be more frequently mutton or goat, lard or vegetable shortening in the Indian, but the significance of this is not immediately obvious. However, the larger proportion of the Navajo Indians eat less fat than the average for the United States, according to his data. The total caloric intake of the Navajo may not be much in excess of 1400 Calories as compared to 3100 Calories for the United States as a whole. Keys[5] suggests that the Navajo diet may be lower in fat content than the average for the United States.

Hereditary factors are less easily studied than current dietary and biochemical patterns which may be related to diet. The Navajo Indian and the larger Athapascan group to which he belongs migrated to the Southwest well after the Pueblo Indian had established himself there. Coming from the North along the Rocky Mountain chain and never learning the arts of farming until comparatively recently, always non-communal in his habits, the Navajo may have had ancestors in whom the factors of natural selection worked with considerable severity. It must also be remembered that the present tribe consisting of some 80,000 individuals are all descended from the 7,500 Navajos who survived the "long-walk" to Ft. Sumner, New Mexico, and the four year imprisonment there in 1864 under less than optimal circumstances. Certainly natural selection was partly at work in determining which individuals would survive this experience. Future studies of other groups subject to attempted genocide may throw some light on the relationship between this type of treatment and the incidence of disease in the survivors and descendants.

The relationship between psychological factors and blood vessel disease is even less well understood and, with our present methods, more resistant to study. The Navajo's religion is neither imperfectly developed nor emotionally unsatisfying by any civilized standards. While it admittedly is losing its influence over the lives of many Navajos, it still provides rather ingeniously powerful rituals for the relief of emotional tensions in many of life's threatening experiences. Its succor is undoubtedly more often sought and found for the average Navajo than either religious or psycho-

therapeutic assistance is sought and found by his white counterpart. Any relation between this element in Navajo life and coronary artery disease can be only conjectural. It is probably also true that the simpler rural life of the Navajo is less competitive than that of the urban American or European.

Exercise factors have not been carefully studied. Whether the Navajo is physically more active than the usual American white city dweller has not been determined, but superficial observation would suggest that he probably is.

SUMMARY

This study was designed to assess more accurately the prevalence of coronary heart disease among the Navajo. From the data presented, it seems that the prevalence of the disease is less by a factor of four or more than that in a comparable age group, namely that group of individuals 31 years of age or older.

The method of approach involved studies of electrocardiographic and autopsy records of Navajo and white hospital in-patients.

Electrocardiographic evidence in this study suggests a lower incidence of coronary artery disease in the Navajo than in the white control group. The pattern of acute myocardial infarction was certainly more frequently seen in the white patients. The differences observed between the two groups in regard to changes diagnostic or suggestive of old infarctions was not as striking.

The autopsy data are considered to be highly significant and indicate a much lower prevalence of coronary heart disease in the Navajo than in a white control group.

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RESUMEN

Se hizo este estudio para estimar la prevalencia de la enfermedad coronaria entre los indios Navajos. Por los datos presentados parece que la prevalencia de la enfermedad es menor por un factor de cuatro, o mas, que el grupo de edad comparable, o sea en los de 31 o mas años.

El método de estudio incluyó estudios electrocardiográficos y protocolos de autopsia de los Navajos y de los internados en un hospital de blancos.

La electrocardiografía en este estudio sugiere una incidencia menor de la enfermedad coronaria entre los Navajos que en los blancos del control. El cuadro del infarto agudo seguramente se vió mas frecuentemente entre los blancos. Las diferencias observadas entre los dos grupos respecto de variantes diagnósticas o sugestivas de antiguos infartos no fueron notables.

Las autopsias se consideran con ser de alta significación e indican una prevalencia mucho mas baja de la enfermedad coronaria entre los navajos que entre los blancos.

RESUMÉ

Cette étude fut entreprise pour déterminer avec plus de précision la prédominance des affections coronariennes parmi la population "Navajo."

La méthode d'investigation comprenait des études électrocardiographiques et des rapports d'autopsies de population Navajo et de malades de race blanche hospitalisés.

Les constatations électrocardiographiques évoquent une fréquence plus basse de l'affection des artères coronaires chez les Navajo que dans le groupe témoin de race blanche. Le tracé d'un infarctus myocardique aigu est certainement plus fréquent chez les malades de race blanche. Les différences observées entre les deux groupes en ce qui concerne les altérations qui permettent le diagnostic on qui évoquent de vieux infarctus ne furent pas aussi frappantes.

Les constatations autopsiques sont considérées comme de grande valeur et indiquent une fréquence beaucoup plus basse de l'affection coronarienne chez les Navajos que pour le groupe témoin de race blanche.

ZUSAMMENFASSUNG

Diese Untersuchung hatte zum Ziel, das Auftreten von Herz-Kranzgefäß-Erkrankungen unter den Navajo-Indianern in New-Mexiko genauer zu ermitteln. Es scheint nach den vorgelegten Angaben, daß das Vorkommen dieser Erkrankung weniger ein Faktor des Alters über 40 Jahre ist, als in einer vergleichbaren Altersklasse, vor allem der Gruppe von Personen im Alter von 31 Jahren und darüber.

Die Methode der Auswertung umfaßte Untersuchungen an Elektrokardiogrammen und Sektionsprotokolle der Navajos und weißer Krankenhauspatienten.

Die elektrokardiographischen Befunde unserer Untersuchung lassen eine geringere Häufigkeit von Kranzarterien-Erkrankungen unter den Navajos vermuten, als unter der weißen Kontrollgruppe. Beispiele eines akuten Myocardinfarktes kamen mit Sicherheit häufiger bei den weißen Patienten vor. Die zwischen beiden Gruppen beobachteten Abweichungen hinsichtlich wahrscheinicher oder vermuteter Veränderungen im Sinne alter Infarkte waren nicht überzeugend.

Es wird die Auffassung vertreten, daß die Sektionsbefunde in beträchtlichem Maße signifikant sind. Sie zeigen eine beträchtlich geringere Häufigkeit von Kranzgefäß-Erkrankungen unter den Navajos als bei einer weißen Vergleichsgruppe.

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The Use of Cardiopulmonary Bypass for the Repair of Atrioseptal Defects and Pulmonary Stenosis*

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With the advent of extracorporeal circulation and the subsequent extension of surgery to defects within the heart, many lesions have become the subject of study and controversy. Several intracardiac lesions are accepted as being best repaired by open cardiotomy. In inter-atrial septal defect and pulmonary stenosis, however, there is still some controversy as to whether the best technique is closed, open using hypothermia, or under direct vision using cardiopulmonary bypass.

There are those clinics in which these lesions are repaired using closed, blind techniques. The difficulty with complicated lesions and the uncertainty of complete repair precludes the acceptance of this approach. This procedure is mentioned only for historical purposes.

Gross and Kirklin have used a semi-closed approach to atrio-septal defects using an atrial well. This requires the defect to be blindly palpated and sutured beneath a pool of blood. It doubtless permits associated smaller lesions to be missed. Gross has subsequently discarded this technique for open atriotomy using cardiopulmonary bypass.

Several clinics have effectively utilized hypothermia as a means of effecting a direct vision repair. This technique emphasized the advantage of repairing an intracardiac lesion under vision, and therefore, was a giant step in intracardiac surgery. However, it has the disadvantage of imposing a time limit upon the surgeon. Although simple foramen ovales defects can be repaired within the accepted limit, there are many complicated lesions which cannot. These include transposed pulmonary veins, transposed inferior vena cava, transposed superior vena cava and high septum secundum defects. It goes without saying that the more complicated ostium primum defects and atrio-ventricular canal cannot be repaired by this technique. Lewis,[1] who has had a considerable experience with hypothermia, has reported a rather high mortality and morbidity with the high septum secundum defects associated with transposed upper and middle lobe pulmonary veins.

We have used extracorporeal bypass with a pump oxygenator for the repair of atrioseptal defects over the past two years, during which time 31 defects were repaired with one mortality. Of these, 16 presented complicated lesions which probably could not have been corrected under a hypothermic technique. There were three high septum secundum defects associated with transposed upper and middle lobe pulmonary veins. One of these presented a transposed superior vena cava requiring a complicated correction, which has been reported.[2] There were two with transposition of the inferior vena cava; two with transposed right pulmonary veins; five with multiple defects; two with cribriform septa; one ostium primum, and one in which a pulmonary valvular stenosis was associated with a transposed pulmonary vein without an associated

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atrioseptal defect. In all, a complete closure was effected using an accurate meticulous repair. The most complicated lesions were repaired without difficulty. To eliminate unnecessary periods of cardiopulmonary bypass, the atria were first explored digitally so that the lesions could be accurately assessed and the technique of repair decided upon. This maneuver led to an expeditious, carefully planned and accurate repair. However, in several cases, although the major defect was palpated by blind digital exploration, multiple smaller lesions were not recognized until the visual inspection. This we believe to be the factor responsible for persistent postoperative arterialization of the right atrium reported by those using closed and semi-closed techniques.

Embryology

At approximately the fifth week of embryonic life, the primitive common atrium begins its separation into right and left chambers. This involves the formation of two septa. The septum primum starts as a crescentic ridge on the dorsocephalic aspect of the atrial wall, and grows toward the atrioventricular canal. Simultaneously, two endocardial cushions, one dorsal, the other ventral, appear in the walls of the atrioventricular canal. These ultimately fuse to divide the atrioventricular canal.

As the septum primum grows toward the atrioventricular canal cushions, the opening known as the interatrial foramen primum, or the ostium primum diminishes in size. At approximately the time that the closure of the ostium primum would have completely divided the atria, a secondary opening develops in the septum primum. This new aperture first appears as multiple small perforations, which subsequently coalesce to form a single, large opening referred to as the ostium secundum.

At the end of the sixth week, a second septum forms which lies just to the right of the septum primum. The ventro-caudal limb of this septum sweeps caudally and merges with the A-V canal cushion to the right of the septum primum. As it grows, its concave margin progressively cuts into the atrial lumen. Its extension gradually ceases and leaves the characteristic oval shaped apperture of the foramen ovale.

The secondary opening in the septum primum was formed so near the cephalic wall of the atrium that the unresorbed lower part of the septum line has a loose flap which covers the oval opening in the septum secundum on its left atrial side and, thereby, forms a one-way valve permitting filling of the left atrium from the right but not vice versa.

Surgical Anatomic Aspects

A. Septum secundum defects are characterized by the fact that the anterior-inferior margin of the defect is formed by a remnant of atrioseptal tissue. These defects may vary in size and location.

B. Septum primum defects are those in the lower portion of the atrial septum in which there is no atrio-septal tissue between the atrioventricular valve ring and the defect.

C. High defects in the septum secundum are located just inferior to the superior vena cava. The superior edge is a sharp crescent which

forms the inferior margin of the defect. Superiorly, the defect has no margin since there is no remnant of septum above it. The defect is superior to, and separate from, the site of the foramen ovale.

Some believe this defect to be due to an abnormal entry of the superior vena cava into both the right and left atria. However, it is probably due to an improper development of the septum secundum which does not cover the resorbed portion of the septum primum. The defect is invariably associated with a partial anomalous pulmonary venous drainage of the right upper and middle lobes. These enter with separate openings into the lower part of the superior vena cava just above the atrioseptal defect.

In our series, the atrial septum has been repaired under direct vision using cardio-pulmonary by-pass. The right atrium has been approached through a right anterior, inframammary incision through the fourth intercostal space with transection of the sternum. The left pleural space has usually not been entered unless the preoperative catheterization suggested the presence of a combined lesion. Early in this series, when complicated lesions were suspected, the heart was approached through a bi-lateral transpleural incision. However, over the past six months, complicated lesions have been approached through a midline sternotomy incision.

The uncomplicated atrioseptal defects are routinely repaired through a right transpleural approach with transection of the sternum in line with the fourth interspace. The pericardium is opened widely by a longitudinal incision anterior to the phrenic nerve. The femoral artery is cannulated, to receive the arterialized blood from the pump. The cavae are cannulated through separate incisions in the atrial wall and the auricular appendage. A purse-string suture is placed around the base of the right auricular appendage and an exploring finger is inserted into the right atrium prior to cannulating the heart. At the time of digital exploration, the lesion is assessed, and the technique for the repair is outlined. The finger is then withdrawn and the superior vena caval catheter is inserted through the tip of the appendage. A second catheter is inserted into the inferior vena cava through a small incision in the wall of the atrium. These catheters are attached to the venous limb of the heart pump.

The patient is then placed on cardio-pulmonary by-pass, the atrium is opened and the repair effected in the beating heart. Cardiac arrest is never used for the repair of atrioseptal defects. Coronary sinus return is aspirated by a low pressure intracardiac suction unit. Before the last sutures are placed in the septal defect, the atrium is allowed to fill with blood and all air from the left atrium is evacuated. The last sutures are then ligated beneath a pool of blood to prevent the collection of a pocket of air in the left atrium. The right atrium is then carefully inspected for the presence of arterialized blood. The presence of arterialized blood at this time indicates the existence of an associated defect. After the defect is repaired, the lips of the atrial incision are grasped, and the inferior caval tape opened. The atrium fills with blood, air is evacuated, and the incision is clamped with a non-crushing clamp. The superior

caval occluding tape is opened, and the patient removed from cardio-pulmonary by-pass. The atrial incision is closed, after which the patient is decannulated. The patient is heparinized with 1.5 mg. of heparin per kilo of body weight prior to being placed on cardio-pulmonary by-pass. Upon completion of the procedure, the clotting mechanism is restored by Polybrene administered in double the heparin dosage.

The heart pump used at this institution consists of a Kay-Cross oxygenator with a DeBakey-type pump. Blood flows from the patient to the oxygenator by gravity. It is then pumped into the femoral artery by a non-occlusive DeBakey-type pump. In this way, the patient is allowed to set his own flow rate. We have found that the flow rates are high and exceed 2400 cc. per meter square per minute. Only at these rates are blood pressures above 80 systolic maintained throughout the periods of perfusion.

In this series of 31 patients, 16 had a simple septum secundum repaired. In this lesion, (Fig. 1) a suture was placed at the upper and lowermost margins of the defect, which was then closed with a running #00 atraumatic silk suture. The line of repair was reinforced with several interrupted figure of eight #000 atraumatic silk sutures.

There were two patients having high septum secundum defects associated with transposed right upper and middle lobe veins into the superior vena cava immediately above its entrance into the right atrium. In these, there was no uppermost margin to the atrioseptal defect and the superior vena cava seemed to straddle both the right and left atria. To properly repair this lesion, an uppermost margin to the defect had to be first created. This was done by running a suture from the uppermost portion of the defect, along the wall of the left atrium, and then into the posterior segment of the superior vena cava just above the transposed veins (Fig. 2). By ligating this suture, an uppermost margin to the defect was created and the transposed veins were redirected into the left atrium. The defect was then closed with a running silk suture. In neither case was it necessary to use a prosthesis, although in one

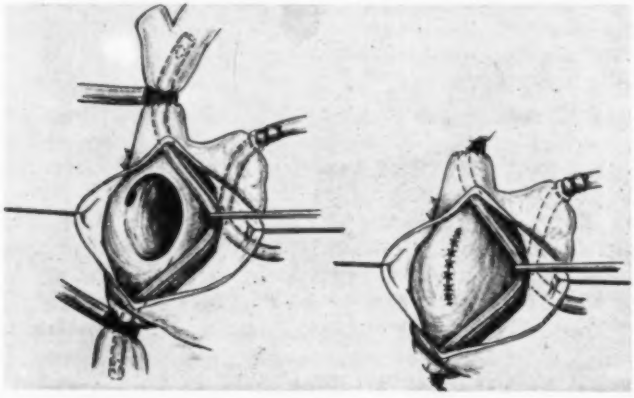

FIGURE 1: The superior and inferior cavae are cannulated. The lesion is closed with a running #00 atraumatic silk suture. The suture line is reinforced with several figure of eight #000 atraumatic silk sutures.

case, the orifice of the superior vena cava into the right atrium was somewhate narrowed.

In one patient, a high septum secundum defect was associated with transposition of the right upper and middle lobe veins into a superior vena cava which itself was transposed, and emptied into the left atrium. In this patient, there was a superior rim to the septal defect. When the defect was closed, the superior vena cava was totally diverted into the left atrium. The right atrium was closed and the superior vena cava was transected proximal to the entrance of the transposed pulmonary veins. This, then, allowed the upper and middle lobe veins to empty into a blind stump of superior vena cava which then emptied into the left atrium. The proximal segment of the superior vena cava was anastomosed to the tip of the right auricular appendage thereby redirecting its blood flow into the right atrium, and effecting a complete repair of the lesion.

In two patients, the atrioseptal defect was associated with a transposition of the inferior vena cava. This lesion was created by a prominent eustachian valve. On palpating the rim of the defect, the finger passed from atrial septum to eustachian valve and then to posterior atrial wall. With a closed technique, one author reported that the vena cava was erroneously directed into the left atrium. Under direct vision, the inferior caval catheter was retracted, thereby enabling the left atrial wall to be visualized. The inferior margin of the septum was sutured, and the suture line then carried across the wall of the left atrium posteriorly to the wall of the right atrium. When this stitch was tied, an inferior rim to

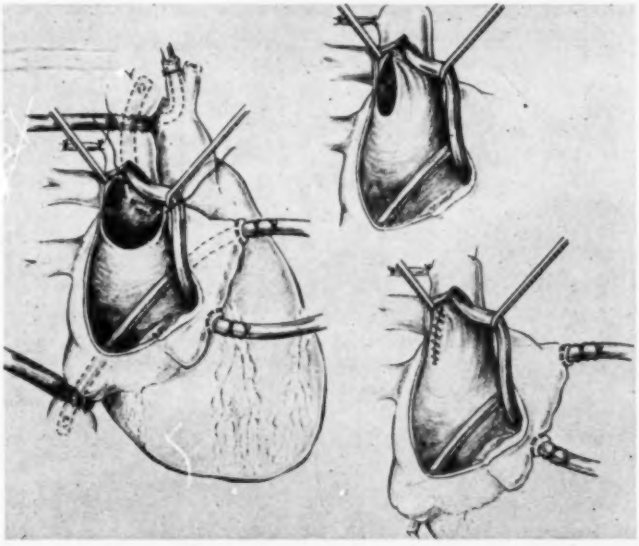

FIGURE 2: An uppermost margin to the lesion is first created. This is done with a continuous suture from the uppermost portion of the defect along the wall of the left atrium and into the posterior portion of the superior vena cava above the transposed veins. When the suture is ligated an uppermost margin to the defect is created and the transposed veins are redirected into the left atrium. The defect is then closed with a running silk suture.

the septal defect was created and the inferior cava was redirected into the right atrium. The atrioseptal defect was then closed by a running suture (Fig. 3). In neither case was it necessary to use a prosthesis for the closure of the defect.

In two patients, there was a transposition of the right pulmonary veins into the right atrium. The lesion was corrected simply by transposing the anterior margin of the atrial septum in the region of the septal defect to the posterior wall of the right atrium, to the right of the pulmonary veins. This type lesion did not present a posterior rim of septum and it was necessary to suture the anterior margin of the septum to the posterior wall of the right atrium. In this way, the pulmonary veins were redirected into the left atrium and the septal defect was totally closed (Fig. 4).

In four patients, multiple defects were found. In each, there was one major defect associated with two or three smaller ones. In two others, the septum was cribriform in nature. In all six, the lesions were closed by a continuous suture to each defect. The cribriform septum was treated as though it were one large defect and was closed with a continuous, running suture. In one, after the cribriform lesion was corrected, arterialized blood continued to emerge into the right atrium. An additional, one cm. defect was visualized anteriorly and inferiorly, well away from the major lesion. This was then closed with a continuous silk suture. In none of these lesions was it necessary to use a prosthesis.

There was one in whom a right pulmonary vein was transposed into the right atrium, and was associated with a small patent foramen ovale in addition to a valvular pulmonic stenosis. In this patient, the pulmonary valvular stenosis was corrected by an open technique, after which the transposed pulmonary vein was corrected under direct vision. This

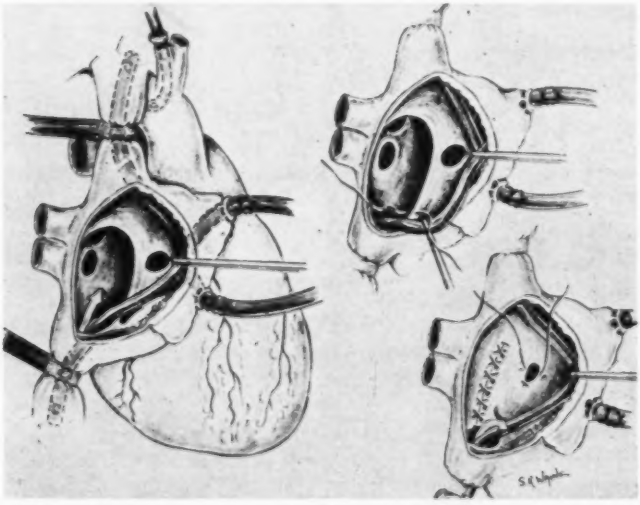

FIGURE 3: An inferior margin to the septum is created by carrying the suture line across the wall of the left atrium posteriorly. The inferior vena cava is redirected into the right atrium, and the closure of the defect completed with a running suture. An associated defect is closed with several interrupted sutures.

repair necessitated the creation of a septal defect at the site of the patent foramen ovale. The septum was then sutured to the posterior wall of the atrium, to the right of the pulmonary veins, which retransposed them into the left atrium, with the complete correction of the lesion.

In this series, many complicated lesions were corrected under direct vision using open atriotomy under cardio-pulmonary by-pass. This technique enables the surgeon to repair these defects using an unhurried, meticulous repair. Since these lesions can be completely corrected using open atriotomy without cardiac arrest, the risk is extremely low.

Pulmonary Stenosis

Pulmonary stenosis, too, has been the subject of much recent controversy as to its best method of repair.

Originally, Brock and Potts led the way in describing a closed technique for the correction of a pulmonary valvular stenosis. This necessitated the introduction of a special knife through the right ventricular wall, into the pulmonary artery. It consisted of incising the valve cusps, thereby converting a pulmonary stenosis into a pulmonary insufficiency. Although it was originally believed that a pulmonary insufficiency seemed not to impose too severe a burden on the right ventricle, it was noted that the surgical procedure was usually followed by by an enlargement of the right ventricle during the postoperative course. Moreover, recently Potts has described several cases of re-stenosis following this blind pulmonary valvulotomy. At most clinics, when the pre and postoperative ventricular and pulmonary artery pressures were monitored, the cardiologists recognized that the right ventricular-pulmonary artery pressure differential was frequently not corrected after the blind tech-

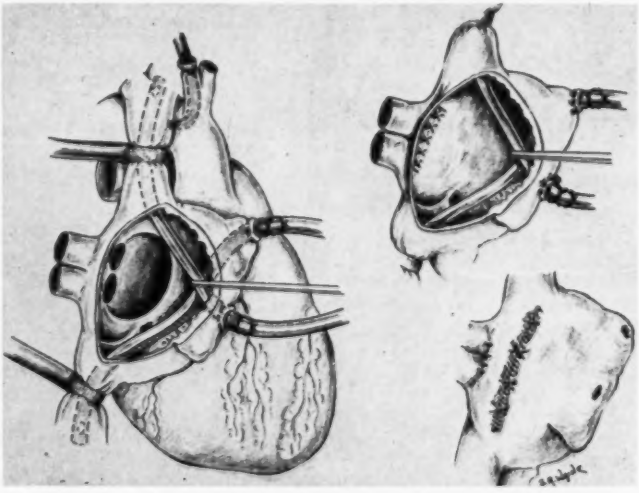

FIGURE 4: The anterior rim of the atrial septum is transposed to the wall of the right atrium, to the right of the aberrant pulmonary veins. This redirects the aberrant veins into the left atrium, with complete closure of the defect.

niques. Swann and others recognized the necessity for repairing this lesion under direct vision and demonstrated the safety of the technique.

Usually a stenotic pulmonary valve is tricuspid. The valve cusps are thickened, and the commissures fused. In some cases, the valve is bicuspid. Invariably, however, the stenotic valve is supported by either two or three commissures. When the repair is effected under vision, the pulmonary artery is opened and the valve leaflets inspected. The stenotic valve is opened accurately and meticulously by incising the fused commissures to the annulus of the pulmonary artery (Fig. 5). The leaflets are thus completely freed, thereby creating a functioning tricuspid valve. In addition, a finger is inserted into the ventricle for the evaluation of the right ventricular outflow tract and to explore for an infundibular stenosis, or a septal defect.

Because of the relative frequency of associated lesions, and, because of our familiarity with the heart pump for cardio-pulmonary by-pass, we have elected to perform these procedures, using an open technique, under cardio-pulmonary by-pass.

We have felt more secure in the knowledge that the heart pump was present to support the circulation in the event of a catastrophe, or cardiac arrythmia. We have not regretted choosing this technique. We have now surgically corrected eight uncomplicated pulmonary valvular stenoses, without mortality. A ninth was associated with an interventricular defect and a tenth was associated with transposed right upper lobe veins and a patent foramen ovale. In the latter case, an atrioseptal defect was created and the septum moved to the right to retranspose the pulmonary veins into the left atrium.

A few years ago, cardiac surgery was unheard of. Over the 15 years, many cardiac lesions were successfully attacked using blind, closed techniques. It was apparent that, if the interior of the heart, itself, were to be inspected and repaired under vision, the heart and lungs would

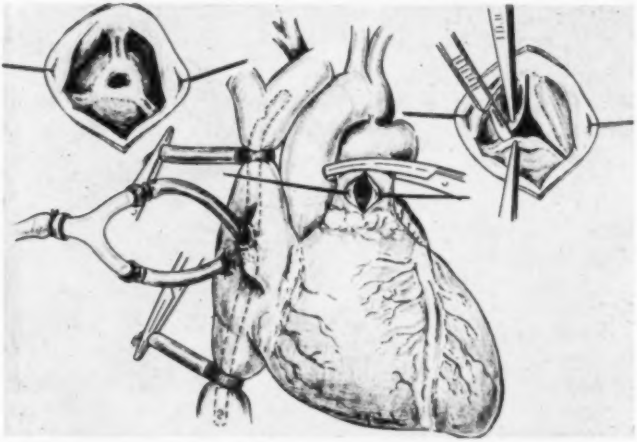

FIGURE 5: The pulmonary artery is opened and the valve leaflets inspected. The stenotic valve is opened by incising the fused commissures to the annulus of the pulmonary artery.

have to be bypassed. It seems obvious that only, under direct vision, can the various lesions be repaired safely and accurately. In addition, the presence of a dependable cardiac pump to support the circuulation in the event of a catastrophe lends added safety to the patient, and confidence to the surgeon.

SUMMARY

1. Extracorporeal circulation with the pump oxygenator has been used for the repair of 31 atrioseptal defects with one mortality. Of these, 16 presented complicated lesions which probably could not have been corrected using a hypothermic technique. In all lesions a complete repair was meticulously effected without difficulty. To eliminate unnecessary periods of cardiopulmonary bypass, the lesions were assessed by a preliminary blind digital exploration.

2. In several cases, although the major defect was palpated by the blind exploration, multiple smaller lesions were not recognized until inspected visually. This, we believe to be responsible for the persistent postoperative arterialization of the right atrium reported by those using closed and semi-closed techniques.

3. In all cases the repair was effected in the beating heart, without arrest.

4. It is believed that congenital pulmonary valvular stenosis, too, is best repaired under direct vision, using extracorporeal circulation. The stenotic valve is supported by either two or three commissures. When the repair is effected under vision, the fused commissures can be incised accurately and meticulously, with the creation of a functioning tricuspid valve. In addition, the right ventricular outflow tract can be explored.

5. Eight uncomplicated pulmonary valvular stenoses have been corrected without mortality. A ninth, associated with an interventricular septal defect, and a tenth, associated with transposed right upper lobe veins, were also corrected without mortality.

Addendum: Since submitting this report 33 additional atrioseptal defects have been operated upon.

RESUMEN

1. Se ha usado la circulación extracorpórea con el oxigenador de bomba en la reparación de 31 defectos atrioseptales con mortalidad de un caso. De estos, 16 tenían lesiones complicadas que probablemente no hubiesen podido corregirse usando técnica de hipotermia. En todas las lesiones se llevó a cabo una meticulosa reparación sin dificultad. Para eliminar los innecesarios períodos de desviación cardiopulmonar, las lesiones se estimaron previamente por una exploración digital ciega.

2. En todos los casos, aunque el defecto mayor fué palpado por la exploración ciega, múltiples lesiones mas pequeñas no se reconocieron sino hasta que se hizo la inspección visual. Esto según creemos es responsable de la arterilización postoperatoria del atrio derecho que se ha relatado porque usan la técnica cerrada y la semi-cerrada.

3. En todos los casos le reparación se llevó a cabo con el corazón latiendo, sin paro cariaco.

4. Se cree que la estenosis valvular congénita también es mejor corregida bajo visión directa usando la circulación extracorpórea.

La válvula estenosada es soportada ya sea por dos o tres comisuras. Cuando la reparación se hace bajo la vista, las comisuras unidas pueden ser seccionadas exacta y meticulosamente creando así una válvula tricúspide capaz de funcionar. Además, el tracto del flujo ventricular derecho puede explorarse.

5. Se han corregido ocho estenosis valvulares complicadas sin mortalidad. La novena, que tenía asociado un defecto septal y la décima asociada con transposición de las venas lobares superiores también se corrigió, siendo ambas sin mortalidad.

RESUMÉ

1. La circulation extra-corporelle avec oxygénateur à pompe a été utilisée pour opérer 31 cas de communication auriculaire. Il n'y eut qu'un décès. Sur ces cas, 16 présentaient des lésions compliquées qui n'auraient probablement pas pu être corrigées en utilisant le simple procédé hypothermique.

Pour toutes les altérations, la réparation complète fut méticuleusement effectués sans difficulté. Pour éliminer des périodes inutiles de circulation artificielle, les lésions furent repérées par une exploration préliminaire aveugle au doigt.

2. Dans plusieurs cas, bien que l'altération principale fût perçue par l'exploration aveugle, de multiples lésions plus petites ne furent pas reconnues tant qu'elles ne furent pas inspectées par vision directe. Les auteurs pensent que c'est là que réside la cause de l'artérialisation post-opératoire persistante de l'oreillette droite, rapportée par ceux qui utilisent des techniques à coeur ouvert ou semi-ouvert.

3. Dans tous les cas, la réparation fut effectuée sur coeur battant, sans arrêt.

4. Les auteurs croient que la sténose dongénitale de valves pulmonaires est également mieux réparée sous vision directe en utilisant la circulation extra-corporelle. La valvule sténosée est soutenue par deux ou trois commissures. Quand l'intervention est effectuée sous vision directe, las comissures soudées peuvent être incisées avec précision et méticuleusement. Ainsi est créée une valvule tricuspide apte à fonctionner. De plus, le flux sanguin du ventricule droit peut être exploré.

5. 8 sténoses de valvules pulmonaires non compliquées ont été corrigées sans aucun décès. Une neuvième, associée à une communication interventriculaire, et une dixiéme, associée à une transposition des veines du lobe supérieur, furent également traitées sans mortalité.

ZUSAMMENFASSUNG

1. Zur Behebung von 31 Vorhof-Scheidewand-Defekten wurde der extrakorporale Kreislauf mit dem Pumpen-Oxygenator angewandt mit nur einem Sterbefall. Unter diesen Patienten befanden sich 16, deren läsion so kompliziert waren, daß man sie wahrscheinlich nicht hätte beheben können, heun man eine Technik der Unterkühlung benutzt. Bei allen Befunden ließ sich eine vollständige Beseitigung ohne Schwierigkeiten peinlichst genau erreichen. Um unnötige Zeitspannen eines kardiopulmonalen Kurzschlusses zu vermeiden, wurden die Befunde durch eine einleitende blinde digitale Untersuchung abgeschätzt.

2. Obwohl die größeren Defekte mittels blinder Untersuchung in mehreren Fällen, zupalpieren waren doch multiple kleinere Veränderungen nicht anders als durch visuelle Inspektion feststellbar Wir glauben, daß dieser Umstand verantwortlich ist für das Fortbestehen der Arterialisation des rechten Vorhofes nach der Operation, die von denjenigen angegeben wird, die von der geschlossenen oder halbgeschlossenen Technik Gebrauch machen.

3. In allen Fällen wurde die Beseitigung des Defektes am schlagenden Herzen ohne Stillstand erzielt.

4. Es wird die Ansicht vertreten, daß angeborene Stenosen der Pulmonalklappe ebenfalls am besten unter direkter Sicht angegangen werden, sowie unter Benutzung des extrakorporalen Kreislaufes. Die stenotische Klappe bekommt durch zwei oder drei Nähte einen Halt. Ist die Beseitigung des Defektes unter Leitung des Auges erfolgt, können die vereinigten Näht sorgsam und gnauestens durchgetrennt werden und eine funktionelle Tricuspidal-Klappe gebildet werden. Außerdem läßt sich die rechtsseitige Kammerausflußbahn untersuchen.

5. 8 unkomplizierte Pulmonal-Klappen-Stenosen wurden korrigiert ohne einen Todesfall. Ein neunter Fall, bei dem gleichzeitig ein Kammerscheidewanddefekt bestand, sowie ein zehnter, bei dem außerdem noch eine Transposition der rechten Oberlappenvenen vorlag, wurden ebenfalls ohne Todesfall korrigiert.

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Experimental Evaluation of Veno-Arterial Pumping, A Proposed Technique for Circulation Support*

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Introduction

The possibility of using artificial heart-lung apparatus for circulation support has frequently been discuussed in recent years[1,2] and Stuckey and his colleagues have reported trial efforts to treat myocardial infarction[3] and congestive heart failure[4] with a conventional pump-oxygenator. Effective circulation support requires a technique capable of providing a considerable proportion of tissue flow requirements for several days. Difficulties will be encountered with both the pump and the oxygenator in such a system.

The roller and finger pumps in use in most heart-lung apparatus damage the formed elements of the blood and the coagulation mechanism[5] so much that they are unsuitable for long-term circulation support. In most types of artificial oxygenators, the presence of a blood-air interface may allow denaturation of plasma proteins,[6] contamination or the entry of air into the system. The membrane oxygenator devised by Clowes and his colleagues[7] avoids this difficulty, but is cumbersome and requires a large volume of blood.

As no satisfactory oxygenator for prolonged perfusion is available at the present time, a system has been designed for artificial circulation support without oxygenation of the blood in the extracorporeal circuit. Blood that has passed through the capillary bed of the upper part of the body is withdrawn from the superior vena cava and pumped without oxygenation into the lower aorta to perfuse the lower limbs and abdomen. The unsaturated venous return from these parts passes via the inferior cava to the right ventricle and so to the lungs for full oxygenation. This system is designated "veno-arterial pumping" and is analogous to the fetal circulation in that the lower half of the body is supplied with partially oxygenated blood that has already been through the capillary bed of the upper part of the body. In the fetus the superior vena caval return passes to the lower aorta via the ductus arteriosus.

The pump used here[8] has ball valves similar to those placed in the aorta in patients with aortic insufficiency. These have been shown to produce little damage to the blood over long periods in vivo.[9] This extracorporeal system avoids the disadvantages of other artificial heart-lung techniques for prolonged circulation support as it is completely closed, the pump is relatively atraumatic and no artificial oxygenator is used. The cardiac output has been measured in 38 experiments in 25 animals.[10] During veno-arterial pumping the cardiac output was always less than the control value. The fall in output was approximately equal to the extracorporeal flow, total body perfusion being unchanged. The extra-

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corporeal flow was between 21 per cent and 72 per cent of total body perfusion. The present report is considered with evaluation of the effects of veno-arterial pumping on the circulation of the dog.

Methods

Fresh dog blood was obtained less than two hours before priming from a single animal lightly anesthetized with 250 to 350 mgm. of intravenous Pentothal. Blood was drawn from the terminal aorta through a cannula in the left femoral artery into collecting bottles containing 10 mgm. of heparin for each 500 ml. of blood and was kept in a water bath at 42 degrees Centigrade until needed.

The subject dogs were male and female mongrels weighing between 11 and 30 Kg. (0.56 and 1.8 M^2 surface area). They were lightly anesthetized with 300 to 500 mgm. Pentothal intravenously without premedication and were secured supine on the operating table. Anesthesia was maintained with supplemental doses of 50 to 100 mgm. of Nembutal intravenously. An endotracheal tube was inserted and connected to a closed circuit spirometer containing 100 per cent oxygen and a carbon dioxide absorber for continuous measurement of the oxygen consumption. Spontaneous respiration was allowed. 1.5 mgm/Kg. of body weight of heparin was given intravenously to each animal. The temperature in the midesophagus was monitored by a Telethermometer.

Bardic cannulae with terminal orifices cut into a fishmouth shape were used to connect the animal with the extracorporeal circuit. The venous cannula was 14 inches (35 cm.) long and varied in size from #18 to #22 Fr. It was inserted into the right external jugular vein and advanced so that the tip was at the junction of the innominate veins. The arterial cannula was six inches long (15 cm.) and ranged from #12 to #18 Fr. in size. It was inserted in the right common femoral artery with the tip in the right external iliac artery. The cannulae were connected by nylon adapters to tygon tubing of ⅜″ (1 cm.) internal diameter which was used throughout the system. Two nylon adapters with side-arm stopcocks were used to fill the apparatus, remove air and obtain samples.

Blood was drained by gravity from the superior vena cava into a collecting chamber placed approximately 100 cm. below the level of the heart. The collecting chamber consisted of a thin-walled, collapsible silicone-rubber cylinder of 200 ml. capacity enclosed in a plexiglass case. Blood passed passively from the collecting chamber to the pump which was a cylinder of heavy silicone-rubber ⅛″ (3 mm.) thick with a high gloss internal finish. The pump chamber was 20 cm. long and had an internal diameter of 2.5 cm. with a capacity of approximately 80 ml. It was enclosed in a rigid plexiglass case of 5 cm. internal diameter. Forward flow was determined by two nylon ball valves mounted in silicone-rubber enclosures at either end of the cylinder.

The pump was operated by pulses of compressed air delivered to the plexiglass case via a pair of reducing valves located in a control box. The first valve reduced the pressure of the compressed air supply to 30 pounds per square inch, and the second valve was adjusted to allow delivery of a fraction of this pressure to the pump and so to regulate

the stroke output. The rate of pumping could be varied from 20 to 180 strokes per minute and compression was applied for half of each cycle. The pump was operated without contact between the walls of the cylinder.

Between the pump and the arterial cannula a coil of tubing passed through a thermostatically controlled water bath which allowed control of the body temperature of the animal. The flow in the extracorporeal circuit was calculated from the time taken for the weight of the collecting chamber to fall 100 Gm. when the inflow line was temporarily occluded.

Polyethylene tubing (PE 205) was inserted in the aortic arch through the left femoral artery, in the inferior cava through the left femoral vein and in the left innominate vein through the left external maxillary vein. In some animals a #7 Cournand catheter was placed in the renal or hepatic vein. Arterial and venous pressures were recorded with Statham P23Db strain gauges and a Sanborn 67 series direct writing 4-channel poly-viso. The base line for all pressure measurements was the table top.

The extracorporeal circuit was primed gravity with 800 ml. blood through one of the side-arm adapters, with the arterial and venous cannulae occluded, while the air in the circuit was allowed to escape through the other side-arm. Residual air was eliminated by circulating blood through a connecting line. The collecting chamber was distended to the limits allowed by the plexiglass case. The connecting line was clamped and the cannulae opened so that blood could drain freely into the collecting chamber. The pump was then started at a rate of 44 strokes per minute and its stroke output increased gradually until the extracorporeal flow reached the maximum allowed by the venous drainage.

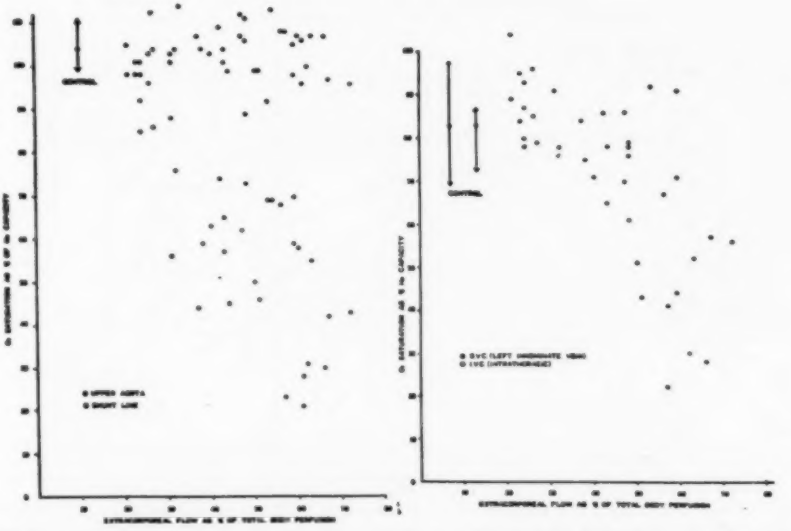

FIGURE 1: Effect of veno-arterial pumping on oxygen saturations; left-upper aorta and shunt line, right—venae cavae.

After 20 minutes veno-arterial pumping at a constant rate arterial blood samples were obtained. Samples were obtained at the same time from the left innominate vein, inferior vena cava, renal and hepatic vein, in various animals. Normal circulation was allowed for 20 minutes before control determinations were made. In some animals observations were made during and after two or three periods of veno-arterial pumping. Blood oxygen contents and capacities and CO_2 contents were determined[11] and oxygen saturation was expressed as a percentage of hemoglobin capacity without correcting for oxygen in solution. Blood pH and hematocrit were measured, and a nomogram designed for human blood[12] was used to derive blood buffer base and pCO_2.

Local arteriovenous oxygen differences were calculated on the asumption that samples from the left innominate vein were representative of the venous return from the head and upper limbs which were perfused with fully saturated blood from the heart, and that the arterial supply to the lower limbs was derived entirely from the extracorporeal circuit. Changes in renal and hepatic vein oxygen contents were used to estimate the proportion of arterial inflow derived from the extracorporeal circuit, assuming no change in the local arteriovenous differences.

Results

Thirty-seven animals were studied. In 11 of these the onset of veno-arterial pumping was associated with the development of a shock-like state characterized by an abrupt fall in blood pressures.[14] In 7 of 11 animals showing this effect the hypotension was not profound, the blood pressure returning to near normal levels in 30 to 60 minutes so that veno-arterial pumping could be recommended without difficulty. No unusual electrolyte or acid base balance patterns were found in the later

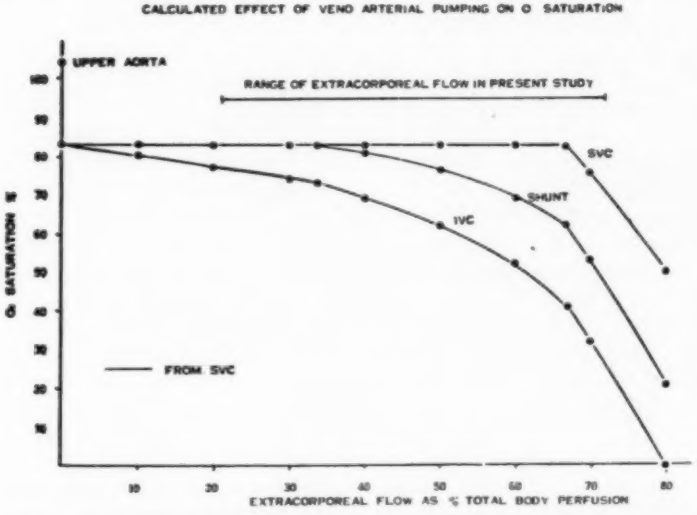

FIGURE 2: Expected effect of veno-arterial pumping on oxygen saturations, assuming that one-third of the venous return is from the superior cava and that local arterio-venous oxygen differences are unchanged by veno-arterial pumping.

blood samples in these animals. In all experiments the mean arterial blood pressure was more than 100 mm. Hg. at the time of study. The body temperatures ranged from 34 to 39 degrees Centigrade and there was no significant difference in temperature between veno-arterial pumping and control periods.

The blood in the aortic arch was fully saturated throughout. In the control periods the oxygen saturation of blood from the left innominate vein (25 experiments in 17 animals) and the intrathoracic inferior vena cava (14 experiments in 10 animals) averaged 83 per cent. The oxygen saturation of blood from these two locations in the venous system and from the extracorporeal circuit tended to fall progressively with increasing veno-arterial pumping (Figure 1). There was considerable overlap between the values from the three sites, the oxygen saturations differing considerably from those expected on the assumption that local arteriovenous oxygen differences were unchanged by veno-arterial pumping (Figure 2). When the volume of the extracorporeal flow was between 40 per cent and 60 per cent of total body perfusion the oxygen saturation in the bypass line was usually between 45 per cent and 75 per cent.

In 25 experiments in 17 animals the arteriovenous oxygen difference across the head and upper limbs was measured. The ratio between the control value and that found during veno-arterial pumping averaged 0.76 (range 0.35 to 1.34). In 14 experiments in 8 animals the arteriovenous oxygen difference could be measured across the lower limbs. The ratio of the control arteriovenous oxygen difference to that during veno-

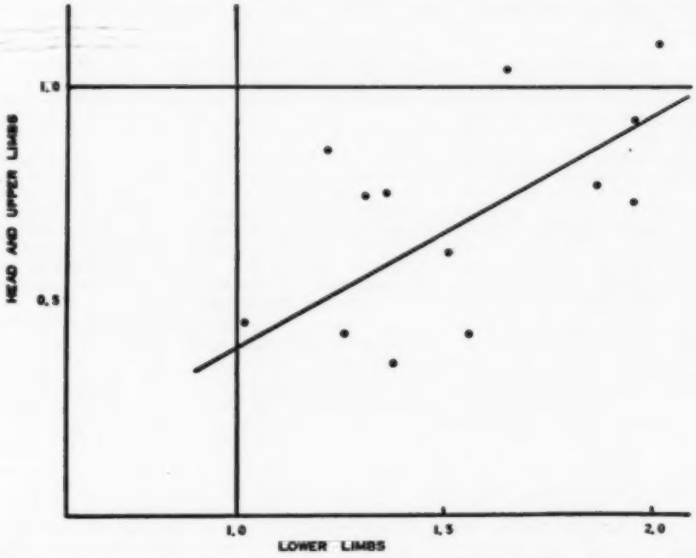

FIGURE 3: Comparison of the changes in local arteriovenous oxygen difference across the head and upper limbs to that across the lower limbs. Changes in arteriovenous oxygen difference are expressed as a ratio of the control value to that found during veno-arterial pumping. If local consumption does not change these figures will also indicate the ratio of the local flow during veno-arterial pumping to the control

arterial pumping averaged 1.51, and was increased in all (range 1.02 to 2.02). These changes were not related to variations in total body perfusion, extracorporeal flow or body temperature. The change in arteriovenous difference in the head and upper limbs could be compared to that in the lower limbs in 12 experiments (Figure 3).

In 4 animals with bypass flows ranging from 48 per cent to 57 per cent of total body perfusion, renal vein saturations indicated that the extracorporeal circuit contributed 80 per cent to 100 per cent of the renal arterial inflow. Similar calculations for the hepatic vein blood in 3 animals with bypass flows from 48 per cent to 54 per cent of total perfusion showed 20 per cent to 50 per cent of the blood supplying the portal system to be derived from the bypass line.

Measurements of the acid base balance were obtained in 40 experiments in 26 animals. An unduly large respiratory dead space was allowed in 19 experiments with consequent CO_2 retention (pCO_2>50 mm. Hg.). The buffer base was always between 30 and 50 mEq/L, and there was no significant change between the control and veno-arterial pumping samples.

Discussion

The system described here provides a simple extracorporeal circuit without an oxygenator that can be used for long-term support of the circulation without undue damage to the formed elements of the blood or the coagulation mechanism. In man, veno-arterial pumping for 16 hours was associated with a plasma hemoglobin level of only 5 mgm. per cent.[16] Falls in the blood platelets are produced but these are maintained between 50,000 and 100,000 per cubic mm. during prolonged perfusion.[15] The system is simple and may be sterilized by autoclaving in a single assembled unit. The tubing is disposable and the apparatus is easily cleaned. It is independent of electrical power and can be operated from a conventional oxygen cylinder.

Rigid control of the blood volume of the subject is provided. The circuit is filled to capacity initially and no significant volume changes are possible. If the venous return is accidentally occluded, extracorporeal flow will cease when the collecting chamber has been emptied, the subject receiving less than 200 ml. of additional blood. If the pump fails venous drainage ceases as the capacity of the collecting chamber is limited. When the pump output is less than the maximum possible venous drainage, the colleecting chamber remains distended and the system will operate for long periods without supervision. The limiting factor to flow is the size of the venous cannula.

Cardiac output is reduced by the volume of extracorporeal flow.[23] The tendency for total body perfusion to fall during veno-arterial pumping in animals with high control values, and to rise in those with control outputs in the lower part of the range, is associated with similar variations in oxygen consumption. It seems, therefore, that the changes in total body perfusion are due to variations in tissue needs rather than to changes in the caliber of arteriovenous communications. The tendency for total body perfusion to rise in animals with a low control flow suggests some initial impairment of cardiac output in these animals. Possible factors are anesthesia, pulmonary collapse, respiratory acidosis and shock following blood exchange.[14]

As the aortic systolic pressure is not reduced, the time-tension index[20] of the left ventricle, total left ventricular wall tension and myocardial work are probably not diminished despite the reduction in stroke output produced by veno-arterial pumping.[21] In the presence of an impaired circulation it is not expected that cardiac output will be reduced or that cardiac work will be changed significantly. It seems likely, however, that total body perfusion will increase as a result of veno-arterial pumping. In the presence of myocardial infarction with shock an increase in total body perfusion may allow recovery of cerebral and renal function without increasing the burden on the heart. Improved coronary blood flow may result from an increase in the arterial pressure with a secondary improvement in myocardial function.

The oxygen saturation of the blood in the extracorporeal circuit is related to the bypass flow. As one-third of the systemic venous return of the dog is contributed by the superior cava,[22] the blood entering the lower aorta would be expected to originate from the superior cava when the bypass flow is less than one-third of body perfusion. As veno-arterial pumping is increased, blood will be drawn into the bypass from the inferior cava. This blood is diverted from the lungs and recirculated through the lower part of the body without oxygenation. The saturation in the bypass and in the inferior cava therefore falls progressively with increasing extracorporeal flow. When

bypass flow exceeds two-thirds of the total body perfusion, some blood from the extracorporeal system enters regions of the body that drain to the superior vena cava, greatly accentuating the fall in oxygen saturation (Figure 2).

The changes in oxygen saturation theoretically expected with increasing veno-arterial pumping cannot be distinguished in the present data. The oxygen saturation of blood in the extracorporeal circuit tends to fall progressively as flow is increased from 20 per cent to 70 per cent of total body perfusion. This may be related in part to the large azygos flow in the dog which will allow blood from the lower part of the body to enter the superior caval system. However, samples from the left innominate vein behave similarly, an appreciable fall in saturation being apparent with a bypass flow less than two-thirds of total body perfusion (Figure 1). The unusually low saturations in the innominate vein are associated with an increase of the arteeriovenous oxygen difference across the head and upper limbs during veno-arterial pumping.

Variations in the local arteriovenous oxygen differences probably indicate local changes in flow. The arteriovenous oxygen difference across the lower limbs is strikingly reduced by veno-arterial pumping, suggesting an increased blood flow in this region and producing an unexpectedly high inferior caval oxygen saturation. The increase in flow in the lower limbs may be related to the opening of arteriovenous communications in the muscles in response to the low oxygen saturation of arterial blood supplied through the extracorporeal circuit. However, animals showing evidence of a reduction in flow in the upper part of the body during veno-arterial pumping have little change in arteriovenous oxygen difference across the lower limbs (Figure 3), indicating that diversion of blood to the lower limbs is not responsible for the changes in flow in the upper limbs and head.

The available evidence from cineangiocardiographic studies,[18] the measurements of oxygen saturation in the aorta at the level of the diaphragm,[15] and the data obtained from hepatic and renal venous samples suggests that mixing of unsaturated blood from the bypass and oxygenated blood from the upper aorta occurs between the diaphragm and the renal arteries when the extracorporeal flow is between one and two L/min/M^2. The oxygen saturation of blood supplying the kidneys, liver and other abdominal viscera is therefore reduced, but no gross evidence of renal or hepatic damage has been noted. The supply of unsaturated arterial blood to the muscles of the lower limbs and back would not be expected to produce significant effects in the resting animal. The absence of changes in buffer base indicates that this local hypoxia does not produce metabolic acidosis.

The data obtained indicate that veno-arterial pumping may be used to provide approximately 50 per cent of total body perfusion. The feasibility of prolonged veno-arterial pumping in animals has been demonstrated in five long-term experiments, the survival of an animal after 52 hours and a patient after 26 hours perfusion being especially encouraging.[15,16] It seems likely that this system could be used in human patients for periods of two to three days without deleterious effects.

SUMMARY

1. A system for circulation support is described in which blood is pumped from the superior cava to the lower aorta without oxygenation.

2. The abscence of a blood-air interface and the atraumatic pump used make the system suitable for prolonged circulation support.

3. The oxygen saturation of blood in the bypass falls with increasing extracorporeal flow. When veno-arterial pumping contributes approximately half the total body perfusion, the unsaturated blood mixes with oxygenated blood from the heart in the abdominal aorta between the diaphragm and the renal arteries.

4. There is evidence of redistribution of blood flow during veno-arterial pumping, flow through the lower limbs increasing and flow through the head and upper limbs tending to decrease.

5. An increase in systemic perfusion and arterial pressure produced by veno-arterial pumping may be effective in relieving shock and increasing coronary blood flow in patients with myocardial infarction.

RESUMEN

1. Un sistema de soporte circulatorio se describe, que consiste en que la sangre es bombeada de la vena cava superior a la aorta inferior sin oxigenación.

2. La ausencia de interferencia sangre-aire y la bomba atraumática usada, hacen el sistema adecuado para una circulación de soporte prolongada.

3. La saturación de oxígeno de la sangre en la desviación cae al aumentar al flujo extracorpóreo. Cuando el bombeo veno-arterial contribuye aproximadamente con la mitad del total de la perfusión del cuerpo, la sangre no saturada se mezcla con la ozigenada del corazón en la aorta abdominal entre el diafragma y las arterias renales.

4. Hay evidencia de la redistribución del flujo sanguíneo durante el bombeo veno-arterial aumentando el flujo en las extremidades y disminuyendo el flujo en la cabeza y extremidades inferiores.

5. Un aumento de la perfusión general y de la presión arterial producida por bombeo veno-arterial puede ser efectivo para aliviar el shock y aumentar en flujo sanguíneo coronario en los enfermos con infarto del miocardio.

RESUMÉ

1. L'auteur décrit un système pour favoriser la circulation qui consiste à aspirer le sang de la veine cave supérieure dans la partie inférieure de l'aorte sans oxygénation.
2. L'absence d'un intervalle sang-air et la pompe non traumatisante utilisée rendent le système convenable pour une aide prolongée à la circulation.
3. La saturation oxygénée du sang dans le court-circuit tombe avec l'augmentation du débit extra-corporel. Quand le pompage véno-artériel contribue approximativement à la moitié de la perfusion totale, le sang non saturé se mélange au sang oxygéné à partir du coeur dans l'aorte abdominale entre le diaphragma et les artères rénales.
4. La preuve d'une redistribution de la circulation sanguine pendant le pompage véno-artériel est fourni par la constatation que le flot sanguin dans les membres inférieurs augmente et le flot de la tête et des membres supérieurs tend à décroitre.
5. Une augmentation de la perfusion organique et de la pression artérielle produite par le pompage véno-artériel peut être efficace en soulageant le choc et augmentant la circulation coronarienne chez les malades atteints d'infarctus du myocarde.

ZUSAMMENFASSUNG

1. Beschreibung eines Kreislaufgerätes, bei dem Blut aus der oberen Hohlvene in die absteigende Aorta gepumpt wird ohne Sauerstoffzufuhr.
2. Das Fehlen einer Blut-Luft-Schranke und die zur Verwenduug kommende atraumatische Pumpe lassen das Gerät für einen längeren Kreislaufersatz geeignet erscheinen.
3. Die Sauerstoffsättigung des Blutes im Kurzschluß fällt mit der zunehmenden extracorporalen Strömungsgeschwindigkeit. Wenn die Pumpenförderung von Vene zur Arterie ungefähr die Hälfte der gesamten Körperdurchströmung ausmacht, vermischt sich das ungesättigte Blut mit dem arterialisierten Blut vom Herzen in der Bauchaorta zwischen Zwerchfelle und dem Abgang der Nierenarterien.
4. Es liegen Beweise vor für eine Wiederausbreitung des Blutflußes während des veno- arteriellen Pump-Vorganges vor, indem die Strömung in den unteren Gliedmaßen zunimmt und durch Kopf und obere Gliedmaßen zur Verringerung neigt.
5. Ein Anstieg der Perfusion im großen Kreislauf und ein Anstieg des arteriellen Druckes, wie er durch den Pumpenvorgang von Vene zur Arterie bewirkt wird, kann von Wirksamkeit sein bei Behebung eines Schocks und zunehmender coronarer Durchblutung bei Kranken mit Myocardinfarkt.

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The Role of Hyperuricemia in Coronary Heart Disease*

The biochemical background of coronary artery disease has been intensively explored in recent years. Hypercholesterolemia *per se* or the one which accompanies diabetes, nephrosis or hypothyroidism have been widely recognized as underlying metabolic disturbances at least for the last two decades. "Essential" hyperlipemia and the increase of certain lipoprotein fractions as well as of the triglycerides[1] have more recently entered the picture. Cholesterol increase in the blood has definitely held the center of the stage, but clinicians everywhere have observed a number of patients with coronary artery disease in whom none of the disturbances mentioned seemed to exist.

Hyperuricemia, on the other hand, has only rarely been brought into relation with coronary artery disease. French clinicians at the end of the last century had already thought of a possible connection between gout and atherosclerosis in general.[2] Roberts has related thromboses to gout.[3] Smyth[4] in the late Forties, compared coronary disease and the uric acid diathesis in terms of genetics, sex distribution, body build and symptomatology. Gertler and White and their co-workers,[5] in their monograph on young adults with coronary heart disease, emphasize the frequent finding of hyperuricemia in this group of individuals (92 patients with an average blood uric acid level of 5.13 ±0.12 and a range of 3.0-7.8 mg. per cent per 100 ml.). Emanuel Libman is quoted as having regarded coronary disease as a manifestation of "gouty diathesis." Traut and his coworkers in 1954 reported a rather unique instance of deposition of uric acid crystals in the walls of the coronary arteries.[6] Sougin-Mibashan and Horowitz,[7] as well as Hansen and Holten[8] and ourselves,[9] in studies of the uricosuric effect of tromexan and dicumarol respectively, have mentioned their observation that hyperuricemia was by no means rare among individuals suffering from coronary heart disease, an impression born out by the recent work of Kohn and Prozan[10] and this author,[11] who both have observed series of individuals bearing signs of this metabolic disturbance. Interestingly enough, Kramer and his associates[12] recently found a high incidence of hyperuricemia in patients with peripheral arterial disease.

Our own key case was a 37 year-old lawyer, whose recovery from a large myocardial infarct seemed to be unduly delayed. Since he had always been a gourmet of some sort, his family had pampered him, especially with chicken liver, during his convalescence. Oddly enough, he had developed all manner of pains which, however, on close scrutiny, turned out to have their exact source in his peripheral arteries wherever palpable. His blood uric acid level then was as high as 13 mg. per cent, and some of his arteries (iliac and tibial, for instance) showed calcifications on x-ray examination. He was put on a purine-poor diet, dicumarol and from time to time, aspirin or probenecid and his condition improved

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considerably. His uric acid blood level has fluctuated for the last three years between 4.8-7.0 mg. per cent. It should be mentioned that this was a non-hypertensive and non-diabetic individual with a normal cholesterol level of his blood throughout, and without evidence of renal disease or blood dyscrasia.

We have recently described another six similar cases, albeit of a lesser degree.[11] These patients, when first presenting themselves with symptoms of coronary artery disease, are usually still comparatively young and are of meso-endomorphic body build. A family history of coronary artery disease, gout or urolithiasis or any combination of these conditions is frequent and on examination of the family we have found other instances of hyperuricemia.

It is a well known observation that some patients will experience an attack of gout after a myocardial infarct, but only rarely is anything known about the pre-infarction blood level of uric acid in these individuals. It is conceivable that the event of an infarct in itself may temporarily raise the blood uric acid level and the immediate post-infarction period therefore may not be the most appropriate time to draw conclusions as to the presence or absence of permanent hyperuricemia in these individuals. Then, patients in hospital are usually put on a coumarin-type anticoagulant which, as has been amply proved,[8,9] represents a very active uricosuric regime. For all these reasons, it is evidently difficult to assess the true incidence of hyperuricemia in patients with recent myocardial infarcts. It may be stated though, that since attention has been focused on this metabolic aspect of coronary disease, the number of such cases recognized by my colleagues and myself in clinical practice, has been on the increase. In recent population surveys designed to study the incidence of coronary heart disease and hypertension in various ethnic groups in this country,[12] we have included uric acid determinations in the blood with the intention of learning something about the incidence of a uric acid level above 5 mg. per cent in various population groups. It seems to us that such uric acid examinations of population samples should profitably be carried out also by others, who do epidemiologic survey studies looking for coronary heart disease and its determinants.

Coronary disease individuals, exhibiting such hyperuricemia, have usually a uric acid clearance within normal limits. The ones we have observed have shown no evidence of any of the other disturbances which may, in their course, produce hyperuricemia, such as renal insufficiency, hemolytic or other blood dyscrasias. All this and their above mentioned family history make this disturbance look to us as a genetically determined abnormality; also, it might well be that their body type would allow for a slightly higher range of blood uric acid, as if a "chemo-type" might correspond to a certain body type. All this goes to say that we might be facing here a biochemical aspect neglected so far, related to heavily built stout people who always have had a reputation of having a tendency to develop gout.

The recognition of hyperuricemic coronary heart disease as a possible sub-entity would have a number of practical consequences. First of all, a determination of the uric acid level in the blood will have to be in-

cluded in the investigation of patients with coronary heart disease. If such an elevated uric acid level will have been found, preferably on several occasions, and other factors such as renal insufficiency and others have been excluded, this finding should be considered significant and consequently lead to action. Our present experience though still rather limited, suggests that we place these patients on a purine-poor diet and add a uricosuric drug in order to bring their uric acid level closer to normal. It is fully realized that such normalization means nothing more than an attempt to correct or at least control a metabolic abnormality, the role of which is still under scrutiny as far as coronary heart disease is concerned. But after all, when we attempt to control the blood sugar or cholesterol level, we are acting very much in similar terms.

Continuous dicumarolization, as frequently used nowadays, may very well act on some of these patients, not only by providing prolonged anticoagulation, but also through its uricosuric effect, taking care at the same time of a possible underlying, though unrecognized, metabolic disturbance. Attempts to establish criteria for a "coronary profile,"[14] i.e. essentially for recognizing constitutionally disease prone individuals,[15] should certainly include a blood uric acid determination beside the customary one of blood cholesterol and lipo-proteins. In such a manner we have found some young people in coronary disease families to exhibit early and still symptomless hyperuricemia.

The recognition that hyperuricemia may be connected with coronary artery disease should affect the management of patients with coronary artery disease and possibly facilitate the earlier detection of disease prone individuals.

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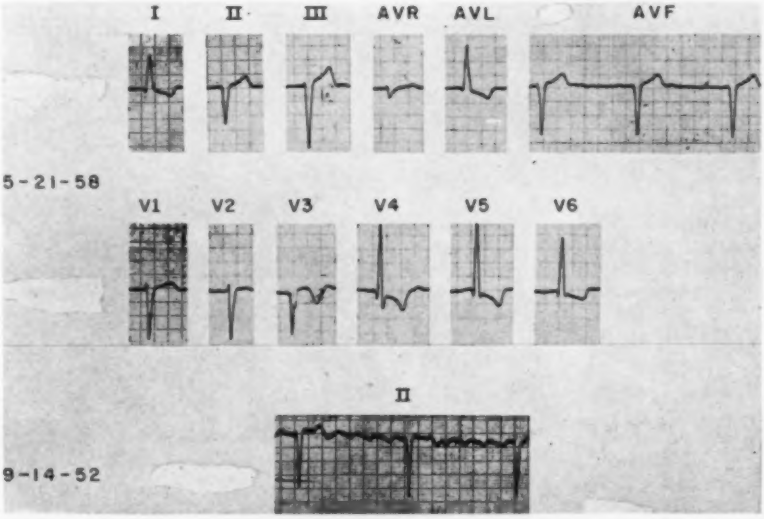
Atrial Flutter and Fibrillation with Complete Heart Block

A 65 year old white male gave the following history. He had chorea at the age of 7 years. When he was 23 years old, he served for two years in the first World War. When he was 43 years of age, he was denied insurance because of a cardiac murmur. At the age of 48 years, he had an attack of syncope followed by a persistently slow pulse. Since that time his blood pressure has varied from an occasional reading of 140/70 to a more frequent recording of 212/95. Congestive heart failure developed for the first time when he was 50 years old and he has been on maintenance digitalis ever since then. Despite that, he had another episode of heart failure at the age of 58 years. When he became 61 years old, he had a myocardial infarct. Examination showed evidence of aortic stenosis and insufficiency with marked left ventricular hypertrophy confirmed by x-ray and electrocardiogram. Serological tests for lues were negative.

The electrocardiogram (Lead 3) dated 9-14-52 (see illustration) shows 6:1 atrial flutter at a rate of 220 beats per minute and a complete heart block with a ventricular rate of 44 beats per minute. The tracing dated 5-21-58 (see illustration) shows atrial fibrillation and complete heart block with a ventricular rate of 44 beats per minute. The absent R wave in Lead V3 is probably due to an old septal myocardial infarct and the depressed ST segments in Leads V4-V6 are partly due to digitalis.



This patient is reported because the presence of either atrial flutter or fibrillation with complete heart block is uncommon. The occurrence of both atrial arrhythmias in the same patient with complete heart block is even rarer. A longevity of seven years after the first bout of heart failure in aortic stenosis and insufficiency is not a common finding and we may speculate that the complete heart block might have exerted a "protective influence" upon the myocardium.

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The Committee on Electrocardiography and Vectorcardiography welcomes comments. We would also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

X-RAY FILM OF THE MONTH

A white woman, aged 93, history unobtainable. She claimed she "did not have a care in the world and never felt better in her life." She was admitted with a Pott's fracture.

Physical examination: slight, aged woman, poorly nourished and developed. Chest: shallow lung excursion, distant breath sounds and no rales; heart sounds distant and of poor quality; A 2 accentuated. Pulse 72, blood pressure 152/100. Extremities, slight pretibial edema, right ankle, Pott's fracture.

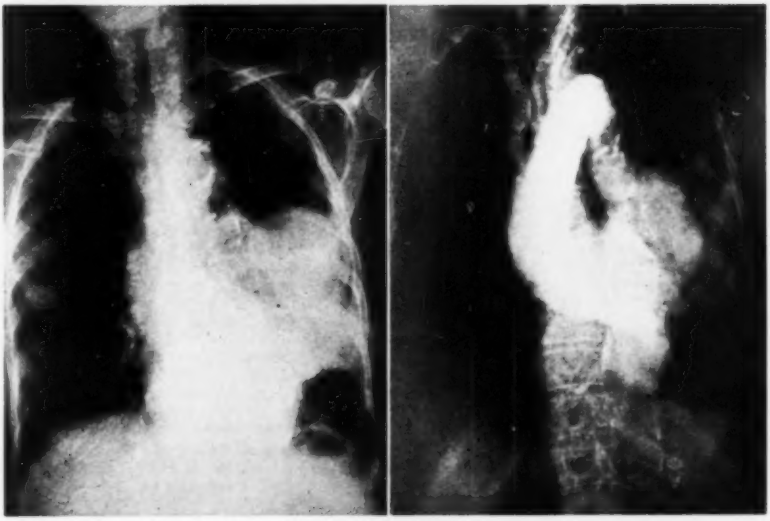
Laboratory reports blood sugar 82.5 mg. per cent. Blood urea nitrogen 29.4 mgm. per cent. Wasserman negative. Kline doubtful.

The course was uneventful until two weeks ago, when she had moderate hemoptysis. Chest at this time was essentially negative, except for moist rales in both bases. Later the same day she brought up copious quantities of bright red frothy blood.

X-ray examination of the chest revealed a large circumscribed area of absent aeration in the central portion of the left lung which extended from the axillary portion of the chest to the hilum, merging with the mediastinal structures. In the lateral projection, this circumscribed area was superimposed over the heart. An aneurysm could not be excluded; the area of diminished aeration was thought to be encapsulated effusion.

Clinically, it was thought that this might be a dissecting aneurysm, or a mediastinal tumor, with the odds on an effusion.

Chest tap yielded blood under pressure. The specimen showed no neoplastic cells, and the culture was negative. The blood count was RBC 3.6 million, Hg. 56 per cent, and WBC 11.000.



At this time an abdominal aneurysm was detected and a re-examination of the chest after two weeks disclosed no change in the findings.

Angiocardiographic examination disclosed a huge aneurysm of the descending aorta with a large mural clot. She expired eight days later. Post mortem examination:

"The patient presented slight to moderate atherosclerosis in its ascending portion of the aorta, there being one focal sclerotic plaque about 2 x 2 cm. just superior to the anterior aortic cusp. There was no wrinkling or tree barking of the ascending aorta. The arch of the aorta began to reveal extensive atherosclerosis with ulceration and superimposed thrombus formation. This process became more marked as one examined distally, so that the descending aorta was practically completely involved by an ulcerating atherosclerosis. About 8 cm. below the arch of the aorta, extending laterally to the left and invading and compressing the posterior aspect of the left lower lobe of the lung, was an aneurysm of the aorta which measured 8 x 6 x 4 cm., and which was lined with a laminated thrombus. No communication could be traced from the aneurysm to the adjacent lung. In the lower portion of the descending aorta, just about 3 cm. above the bifurcation into the common iliac vessels, were found two small aneurysmal outpouchings, each measuring 2 x 2 cm., and each lined with a laminated thrombus.

Microscopic examination of the aorta revealed a questionable leutic aortitis.

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The Committee on Chest Roentgenology welcomes comments. We would also be pleased to receive x-ray films of exceptional interest with brief history. Please submit material to: Benjamin Felson, M.D., chairman, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio.

Case Report Section

Report of a Case of Diffuse Interstitial Pulmonary Fibrosis

("Hamman-Rich Syndrome")

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During 1954, the following case of Hamman-Rich Syndrome was admitted to Fitzsimons Army Hospital. We are reporting the findings so that the accumulation of data in the literature may ultimately lead to a more complete understanding of this condition.

Case Report

A 41 year-old white man was admitted to FAH on October 25, 1954 from USAH Landstuhl, Germany, complaining of soreness of the chest.

He stated he "felt perfectly well" until June, 1954, when he noticed the onset of increasing fatigability. During the next three months, he lost 15 pounds in weight. About September 1, 1954, a generalized aching and soreness developed in his left chest laterally, and over the left base posteriorly. This gradually increased to a generalized tightness of the entire chest. Two weeks later, a slight cough developed, productive of about one tablespoonful of clear mucous daily. With the onset of cough, there was a change in character of the chest pain: it had become pleuritic. This was accompanied by fever, night sweats, and dyspnea on exertion. There was no history of hemoptysis or wheezing. On September 18, 1954 he reported to the dispensary, where a chest roentgenogram was taken and read as suspicious of pulmonary tuberculosis. He was immediately hospitalized at the 97th General Hospital in Germany. Repeated sputa examinations were positive for acid-fast bacilli by smear. On September 23, 1954, streptomycin, 1 gram every third day and isoniazid, 300 mgs daily were started and continued to July 3, 1955.

He denied all other illness, except "pneumonia" in 1951 while in Korea, for which he was not hospitalized and no x-ray films were taken. He was treated on quarters with Aurcomycin, and returned to duty after a few days without further symptoms.

Prior to entering the Army, he worked as a farmer. In the military service, he worked as a supervisor in garages where painting and remodeling was done to Army vehicles. The work was supervisory and he was never exposed to paint spraying. During 1951 and 1952, there was periodic breaking of fluorescent lights within the shop; averaging two to four times weekly. He denied close contact to any of these incidents.

On examination he was a well developed, and well nourished white man of 41, who did not appear acutely or critically ill. His temperature was 98.6° F; pulse, 70 per minute; respirations, 17 per minute; blood pressure, 110/80.

He was a small, slender white man who appeared 8 to 10 years older than his stated age. There was moderate clubbing of all fingers which he thinks has been present for many years and he recalled that two siblings have similar fingers. Pleural friction was elicited over the left lower chest laterally. Extensive post-tussive rales were heard over the left lower third of the chest bilaterally without regard to lobar distribution. Breath sounds were decreased over the left lower chest with impaired resonance to percussion in this area. Chest expansion seemed normal on both sides. Vital capacity was two liters, 66 per cent of the predicted and slow. No other abnormal findings were noted.

Purified protein derivative first strength and histoplasmin (1:100) were positive; coccidioidin (1:100) was negative. Serology for histoplasmosis, blastomycosis, and coccidioidomycosis were negative. The white blood cell count was 16,850; 63 per cent neutrophils, 31 per cent lymphocytes, 4 per cent monocytes, and 2 per cent eosinophils. They were with 5.26 million red blood cells. The erythrocyte sedimentation rate was 15 mm/hr. Hematocrit 50 mm. Urine normal. Sputum specimens collected during October, November and December, 1954 were repeatedly positive for tubercle bacilli by concentrated smear and culture. Sputa collected during the same period were negative by culture for fungi. Repeated sputum speciemns collected from January through June, 1955 were negative by concentrated smear and culture for tubercle bacilli. Bronchial washings were negative for malignant cells.

A review of chest x-ray films taken in 1945, 1948, and 1949 revealed a small, round, calcific density in the lower left lung field and calcium deposits in the left hilum

From the Pulmonary Disease Service, Fitzsimons Army Hospital

region. Otherwise, the heart and lungs appeared normal. The first "positive" x-ray film, dated September 18, 1954, revealed a hazy density obscuring the lower one third of the left lung field, with soft nodular densities in the third anterior interspace on the left and a finely reticulated pattern throughout all lobes of both lungs. The mediastinum and heart appeared within normal limits. The calcific densities seen on previous films were present and unchanged. Lateral and oblique views revealed that the homogeneous density seen on the routine postero-anterior x-ray film was confined principally to the lingula of the left upper lobe. The reticulated pattern described in the postero-anterior x-ray film throughout the remainder of the lung fields was particularly prominent on the lateral and oblique views. He had diffuse disease scattered throughout all lobes of both lungs.

Serial monthly roentgenograms through May 27, 1955 revealed no clearing. Instead, there had been a generalized progression of the disease. The reticulated pattern had increased in all lobes of both lungs, and numerous, small, soft nodular densities had developed throughout both lung fields.

Bronchoscopy, on October 28, 1954, revealed on the right a small tubercle superior to the middle lobe orifice and another small tubercle superior to the anterior basilar segmental orifice. The left lower lobe bronchus was mildly stenotic, permitting the passage of a 7 mm bronchoscope with difficulty. Granulations were seen in this area. Bronchial washing cultures were positive for M. tuberculosis and negative for fungi. Bronchoscopy on May 3, 1955 revealed no endobronchial disease.

The organisms were sensitive to streptomycin and isoniazid which were started on September 23, 1954 and continuel until July 3, 1955. After eight months of anti-microbial therapy for tuberculosis the sputum had been negative for acid-fast bacilli for five months, but the roentgenograms showed progression of the lesions in all lobes of both lungs.

At conference on June 16, 1955 the history and clinical course were reviewed. Except for the possible exposure to beryllium, nothing significant was found. Physical examination revealed a chronically ill-appearing, white man, with slight dusky hue to his face and slight cyanosis of the lips and ear lobes. Cyanosis of the nailbeds and marked clubbing of all fingers and toes were present. There was marked dyspnea after walking up one flight of stairs. The chest appeared to expand equally bilaterally. Decreased resonance and pronounced post-tussive rales were found at the left base posteriorily. Heart appeared to be normal. Abdominal examination was within normal limits.

The pulmonary tuberculosis, documented by 10 positive sputum examinations over a four month period, apparently was adequately controlled. The fine lacey reticulated pattern seen in the chest roentgenogram had increased, so this was probably due to a second and actively progressive disease process. The interstitial nature of the lesion, and the possibility of alveolar-capillary blocking made consideration of a large number of disease entities mandatory. However, possibility was reduced to fungus infection, neoplasm, beryllium granulomatosis, and Hamman-Rich Syndrome. The following studies were done to assist in making a definitive diagnosis:

1. Three sputum specimens examined for tumor cells: Negative.

2. Bronchial washings examined for tumor cells: Negative.

3. Bronchial washings cultured for fungi: Negative.

4. Laminograms revealed a fine, lacey network throughout all lobes which was interpreted to suggest fibrosis and emphysematous blebs.

5. EKG on June 20, 1955 was within normal limits. No evidence of right heart strain.

6. Oxygen saturation tests: Resting arterial O_2 saturation 71 per cent. The standard bicycle exercise was planned for six minutes, but after two and one half minutes extreme dyspnea and fatigue developed, so it was stopped. Approximately one minute later a sample of blood from the right femoral artery revealed O_2 saturation of 65 per cent.

On June 24, 1955, following walking down and up one flight of stairs, he became extremely dyspneic and was relieved by lying flat in bed. This was accompanied by the development of a slight hacking cough; mild precordial pain which disappeared with rest; marked cyanosis of lips, earlobes, and nailbeds. Blood pressure was 117/80; temperature 99.4°; pulse, 120/min.; respirations, 28/min.; dyspnea and cyanosis persisted. Three hours later he developed fever of 102°F, pulse 140/minute, respirations 36/minute, and blood pressure 120/80. There were moist rales throughout both lung fields. The liver was not palpable and there was no ankle edema. An EKG revealed a rate of 150/minute, with a slight change in the electrical position and slight elevation of the ST segments over precordial areas when compared with a previous EKG. There was no evidence of myocardial infarction.

He was definitely more comfortable lying absolutely flat in bed. The neck veins were not distended. He was treated symptomatically and observed closely. Aminophyllin grs. IV intravenously, mercurophylline 1 cc intramuscularly and morphine sulphate grs. ⅙ subcutaneously were given. He became comfortable and slept well throughout the night.

The following morning the temperature was 98.6°F, pulse 124/minute, respirations 28/minute, and blood pressure was 104/76. Rales were present at both bases, but the upper lung fields seemed to be clearer. The cyanosis had markedly decreased. There was no detectable enlargement of the liver and no ankle edema. There was no tenderness of the calf muscles and pulsations in femoral regions were equal and forceful. Laboratory studies revealed: white blood cells 15,600; PMNS 76 per cent, lymphocytes 20 per cent, monocytes 2 per cent, and eosinophils 2 per cent. There were 6.34 million red blood cells. Hgb 17.2 grams per cent. Hematocrit 55 mm. Bleeding time 20 seconds, coagulation time eight minutes. Chest film revealed no change from previous serial films. He rested comfortable for the next five days so long as he remained in bed, but any slight exertion caused extreme dyspnea. On June 30, 1955 the consensus of opinion was that he had multiple pulmonary emboli and pulmonary edema. Coumedin 75 mgms was administered.

Following examination, the cardiologist stated that he doubtedly had pulmonary hypertension, probably on a chronic basis. In addition there had been some additional insult to the pulmonary circuit, most likely on the basis of a small pulmonary embolus. The EKG's were in keeping with right ventricular ischemia, probably of the strain pattern, although subendocardial infarction of the septum could not be ruled out. The whole picture was more in keeping with the former. Although there was no evidence of right heart failure at the moment, it probably was incipient. It was thought he should be digitalized and the anticoagulant therapy continued.

At noon digitoxin 0.6 mgm was given. Throughout the afternoon and early evening there was no change, but at 2000 hours, respirations increased to 40/minute, pulse 120/minute, and temperature 100.8°F. Digitoxin 0.2 mgm was given and oxygen, by face mask, at five liters per minute was started. After five minutes, respirations decreased to 18/minute and cyanosis markedly decreased. He stated he felt much better. During the remainder of the night, the dyspnea and cyanosis were markedly relieved by intermittent oxygen, and he slept for long intervals. Continuous oxygen therapy in a tent was instituted the following morning.

His condition remained unchanged under supportive therapy until the afternoon of July 3, 1955 when there was a sudden increase in dyspnea. This was accompanied by evidence of venous engorgement and slight tenderness in the liver area, although the liver was not palpable. It was our impression that he had cor pulmonale with heart failure.

Two hours later he began to gasp for breath and stopped breathing within a few minutes.

CLINICAL DIAGNOSES:

1. TUBERCULOSIS, pulmonary, far advanced, bilateral, all lobes.
2. FIBROSIS, pulmonary, interstitial, unknown etiology.
3. ENLARGEMENT OF THE HEART due to pulmonary disease (cor pulmonale).

An autopsy was performed on July 4, 1955 and the following significant pathologic findings, gross and microscopic, were observed:

GROSS: There was no fluid in either thoracic cavity. The right lung was free; the left lung was bound down by fibrinous adhesions in all areas. These adhesions can be broken easily by hand.

The right lung weighs 970 grams, the left 580 grams. Both lungs were firm to palpation but crepitant. On the external surface of each lung were multiple solid pink nodules extending above the surface of the red-blue background. At the apex of the left lung were several small blebs, the largest measuring 0.7 cm in diameter. There were several fairly firm areas in the neighborhood of the lingula. On probing the bronchi, there was no evidence of endobronchial disease except in the left lung. There were several nodules encroaching upon the lingular bronchus and compressing blood vessels in this area. The bronchi to the left lower lobe did not appear to be encroached upon, but the nodules in the lingula extended to this area. Examination of the pulmonary vascular tree revealed no evidence of thrombosis, embolism or infarction of lung parenchyma. The parenchyma is moderately edematous in both upper lobes, and there is congestion of a moderate degree in both lower lobes. Section of lung parenchyma revealed diffuse fibrosis, emphysema, and greyish discoloration throughout. Although the lungs floated in water, there was little available space for respiration to occur. The heart weighed 365 grams and the right ventricular wall measures 0.4 cm in thickness, which for an individual weighing 135 pounds, probably represents mild hypertrophy. The liver and spleen were markedly congested.

There were several nodes at the hilus of the left lung measuring approximately 2.0 cm in diameter and one lymph node at the carina measuring 4.0 cm in diameter. These nodes were soft with no calcific areas palpable. Section reveals a mottled grey cut surface.

Eight sections of lung showed essentially the same changes: the bronchi in some areas had preserved their cuboidal epithelium, but in most areas bronchial epithelium was denuded. Bronchioles in most areas had preserved their epithelium, and in many areas bronchiolar epithelium was seen to have extended to line the alveoli. In many

areas this epithelium had undergone squamous metaplasia. Almost all the alveoli were airless, and were filled with blood in some areas and with pigment-laden macrophages in others. In some areas the alveolar exudate was undergoing organization by fibrin deposition and occasionally by fibroblastic proliferation, and here occasional multinucleated giant cells were seen. The alveoli which were not lined by the bronchiolar or squamous epithelium were lined by a homogenous hyaline-like membrane. The interstitial tissue of the lung showed increased fibrous tissue, fibroblastic proliferation and neovascularization. Inflammatory change was minimal and consisted of a few monocytes. The pleura did not appear to be thickened but the diffuse lesion previously described extended up to a subpleural location. Four sections stained for acid-fast bacilli were negative. Stain for iron was also negative.

Sections of four lymph nodes removed from the thorax showed essentially the same picture. The capsules were intact. Germinal centers were visible but were considerably distorted by a marked congestion associated with an ingrowth of new blood vessels. There was also a moderate increase in fibrous tissue. A generous amount of anthracotic pigment was present. On one slide four old, healed granulomata were seen, but their etiology was not known.

The pathologic cause of death was diffuse interstitial fibrosis of the lungs of the type described by Hamman and Rich. The immediate cause of death was acute right heart failure. The entire case was reviewed by the Armed Forces Institute of Pathology and the diagnosis of Hamman-Rich Type of diffuse interstitial pulmonary fibrosis was confirmed.

Discussion

Extensive pulmonary fibrosis as a cause of respiratory insufficiency may appear in several different forms and have many different causes. The original description of the Hamman-Rich type of diffuse interstitial pulmonary fibrosis remains essentially unchanged. However, it is now known that the disease may run a protracted course, and that the apparently acute fulminating cases may be the terminal phase of a more chronic illness.

The present case is interesting in that the admission diagnosis was proved pulmonary tuberculosis. Repeated sputum cultures during the first four months were all positive for acid-fast bacilli, which morphologically and culturally resembled M. tuberculosis. However, throughout the remainder of hospitalization the sputum was persistently negative for acid-fast bacilli. The patient had received more than nine months of continuous anti-tuberculosis chemotherapy, which apparently accounted for the permanent conversion of the sputum and the absence of pathologic evidence of tuberculosis. The only possible remote evidence of tuberculosis infection was "healed granulomata of unknown etiology" seen in one section of a lymph node.

Whereas, after eight months of treatment, the tuberculosis had been apparently controlled, the roentgenographic findings remained unchanged. It was this fact that lead us to the conclusion that the reticulated pattern seen throughout all lobes of both lungs was probbaly due to an interstitial pulmonary fibrosis of unknown etiology. The second diagnosis was not established until after necropsy.

Although the clinical course and roentgenographic findings are characteristic during the late stages of Hamman-Rich Syndrome, the diagnosis can be established only by histologic examination. Furthermore, it must be borne in mind that there are numerous other diseaes entities which can produce similar clinical and roentgenographic patterns.

Although the cause of this disease is unknown, many theories have been postulated but none has been proved. Bacteria have not been demonstrated in the lesions. No common chemical irritant or occupation has been identified. The lesions do resemble those seen in influenzal and atypical pneumonias. The possibility of a hypersensitivity or allergic reaction, or a nonspecific reaction initiated by a variety of substances have been suggested as etiologic agents, but the cause still remains unidentified.

Reticulum Cell Sarcoma of the Thorax In A Two-Week-Old Infant

Associated with Staphylococcal Empyema

A REVIEW AND CASE REPORT

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Reticulum cell sarcoma is relatively uncommon in childhood and apparently, no case of the lymphosarcoma group, occurring in the thorax, has been reported at such an early age as the case presented here.

Gall and Mallory[6] divided reticulum cell sarcoma into two types: (1) stem cell sarcoma, and (2) clasmatocytic lymphoma. Hellwig's[7] classification suggested reticulocytoma for (1) and monocytoma for (2). Hazel and Jensik[4] described 12 cases of lymphoma, including one of reticulum cell sarcoma, of the lung and pleura. Gall and Mallory,[5] among 618 cases of malignant lymphoma, reported 127 instances of reticulum cell sarcoma; about 16 per cent of the patients had hydrothorax, 25 per cent had mediastinal lymph-node involvement and 6 per cent had pulmonary involvement.

Case Report: J.P.A., a three-week-old French Canadian boy, was admitted to the Ottawa General Hospital because of rapid and difficult breathing, which had begun one week earlier. The baby had occasional cough without cyanosis. His milk intake had decreased and his breathing would become more laboured after feeding. He was the first born of healthy unrelated parents; the pregnancy had been uneventful, the delivery was normal and full term. The mother had undergone x-ray pelvimetry two weeks before the birth of the child. The birth weight was 3600 grams. The baby was given BCG by scarification on both deltoid areas two days after birth. During the first week, he had minute pustules over the abdomen and legs.

On physical examination, the infant was of average build, restless and dyspnoeic, but without cyanosis. The temperature was 37.2°C (rectal), the respirations were laboured (rate about 70/min.), the heart rate was 180/min. The heart was shifted to the right side and the heart sounds were heard only on the right side. The trachea was deviated towards the right side. The left side of the chest was bulging, and there was fullness of the intercostal spaces. Movements of the chest were greatly diminished on the left side. The breath sounds were completely absent over the whole of the left chest which was stony dull on percussion. On the right side, no adventitious sound was heard and there was no dullness. There was no palpable lymph node on admission. The spleen was just palpable. There was no evidence of free fluid in the peritoneal cavity. Other systems were unremarkable.

Skiagram of the chest showed massive pleural effusion on the left side. An immediate thoracentesis was performed and 85 cc. of slightly turbid yellowish fluid were aspirated. Tetracycline was injected intrapleurally and also prescribed parenterally. The examination of the pleural fluid revealed gram-positive cocci on the smear and it grew haemolytic *staphylococcus aureus* (coagulase positive) on culture.

It was evident that the infant had staphylococcal empyema on the left side and was treated accordingly. After several thoracenteses, the clinical and radiological improvement was obvious. The pleural fluid quickly became sterile. Streptokinase and streptodornase were administered intrapleurally after thoracenteses. At the end of a week, a skiagram showed well-defined opacities in the upper and lower lung fields on the left side (Fig. 1). These opacities were considered to be adhesions or masses of fibrin and thickened pleura, as a result of staphylococcal empyema. There was no pneumothorax. Scant amount of fluid could be aspirated from the left pleural cavity, although the mediastinum was still displaced towards the right.

During the second and third weeks of hospitalization, the respiratory distress increased on several occasions which was, to some extent, relieved by thoracenteses.

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In the fourth week of hospitalization, the general condition deteriorated, the dyspnoea persisted and the area of dullness on percussion, on the left side of the chest, increased in extent along with more mediastinal shift towards the right side. No fluid could be aspirated by thoracentesis. There appeared oral thrush, diarrhea and maculopapular rash over the face.

At the end of the fourth week of hospitalization, the skiagram showed massive mediastinal shift towards the right side, so that almost the whole chest was opaque (Fig. 2). The baby was extremely dyspnoeic and frequently cyanosed even in oxygen. At this point, the possibility of a thick exudate was entertained, and a costotomy was carried out. The pleural cavity was seen to contain a matted, sponge-like substance resembling fibrin, with little serosanguineous exudate. Under-water-seal drainage of the cavity was installed, but only scanty exudate was obtained.

On the next day, the 28th after admission, the child experienced increasing dyspnoea, cyanotic attacks, Cheyne-Stokes breathing, and died in a state of asphyxia. During the hospitalization, the infant received tetracycline, streptomycin, erythromycin, mycostatin, cortisone and plasma and blood transfusions.

At autopsy the body weighed 3100 grams. On external examination, a few hard lymph nodes were felt in the left axilla. There was no lymphadenopthy in the remaining areas. The thorax was bulging on the left side. The pericardial cavity was filled with 150 cc. of clear yellow fluid. The anterior pericardium appeared normal. The posterior pericardium was adherent to the large mass which had apparently replaced the whole mediastinum and infiltrated the leaves of the diaphragm, protruding into the retroperitoneum (Fig. 3). The mass extended laterally from the posterior mediastinum towards the ribs and alongside the whole left thoracic cage. It had completely surrounded the left lung and had apparently spread into the left axillary lymph nodes. The right pleural cavity and the right lung were normal. The left thoracic cavity was completely obliterated by a light, fatty-appearing, greyish mass of soft consistency, the extent of which has been described. The larynx, trachea and bronchi were normal on the right, but obliterated and continuous with the mass on the left. The peritoneal cavity contained a small amount of clear yellow fluid. The bone marrow of the ribs appeared normal. The rest of the examination was apparently normal.

On microscopic examination, the lungs were atelectatic, particularly on the left side. The tumour was a small-celled, undifferentiated, moderately reticulum-producing mesothelial neoplasm (reticulum cell sarcoma) (Fig. 4). The lymph node from the left axilla showed infiltration by tumour. The heart, liver, spleen, pancreas, adrenals, kidneys and bone marrow were normal (Prof. D. Magner).

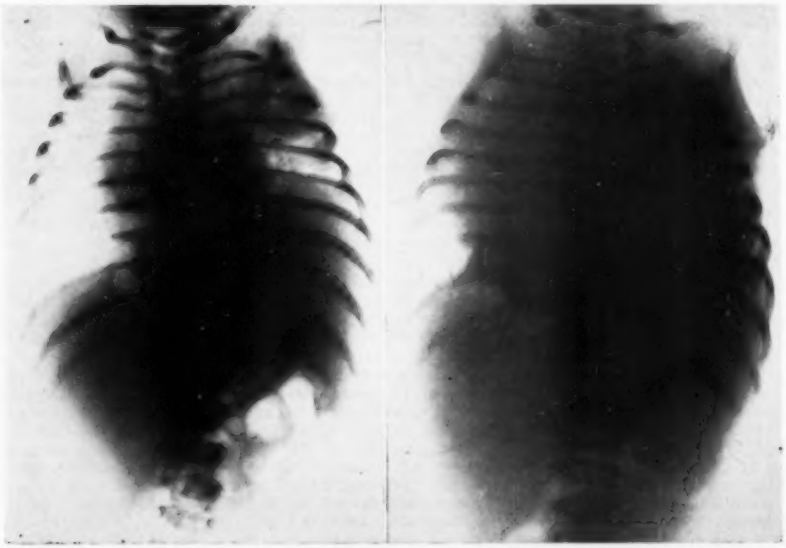

FIGURE 1: Postero-anterior roentgenogram of the chest, showing well defined opacities in the upper and lower lung fields on the left side, after several thoracenteses.

FIGURE 2: Postero-anterior roentgenogram of the chest, showing massive shift of the mediastinum towards the right side, so that most of the chest appeared opaque, a day before the death of the infant.

Discussion and Comment

This case was first diagnosed as a staphylococcal empyema. The presence of infection masked the clinical picture of reticulum cell sarcoma of the thorax. The peculiar and spongy character of the masses brought fleetingly to mind the possibility of a tumour, but the diagnosis of intrathoracic malignancy, which is extremely rare at this early age, was not made until the autopsy examination, when the infant died at the age of seven weeks.

Early recognition of reticulum cell sarcoma is of paramount importance for a more effective treatment and a better prognosis. Thoracic symptoms in only 3.6 per cent of the cases were the first indications to be noted in 196 cases of lymphosarcoma.[15] The diagnosis of reticulum cell sarcoma has been made by bronchoscopic biopsy[6] or by pulmonary biopsy.[6] In Brunner's[2] case, the tumor looked like "placenta" with blood clots, whereas in our case it looked like "sponge." Pleural biopsy is of value. Mathur and Zaidi[9] (one of us) reported a case of mesothelioma of the pleura in an adult where diagnosis was confirmed by needle-biopsy of the pleura. The value of a contrast visualization of the venae cavae has been demonstrated.[12]

FIGURE 3: Anterior view of the left side of the chest on autopsy, showing the tumor (T) occupying the left pleural cavity, infiltrating the leaves of the diaphragm (D) and protruding into the retroperitoneum. The lung (L) and the heart (H) have been pulled upwards and to the right.

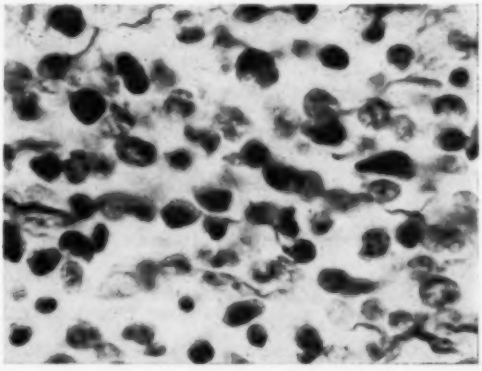

FIGURE 4: Photomicrograph showing the microscopic appearance of the small-celled, undifferentiated reticulum-producing neoplasm. (Reticulum Stain; X650).

Instances of a "leukaemic" terminal phase has often been observed.[3,11,16,17] That this change should happen is puzzling, from the etiological standpoint, in view of the finding of Stewart and her co-workers[13] that in children with leukemia and those with various types of malignant tumors, exposure to x-rays during gestation had been almost twice as frequent as for control children, *except* in the group with lymphatic tumors.

The average age of onset is about 45 years. A patient aged 107 years was recorded.[15] Instances of lymphosarcoma of the mediastinum, in infancy, were observed by De Lange and Von Goor (quoted by Branch[1]), Rogartz (quoted by Dargeon[3]), and others;[8,14] and in childhood, by Wiglesworth *et al.*[17] (3 cases) and Mukerjee[10] (one case). Berghinz (quoted by Dargeon[3]), observed it in the liver of the one-day-old infant of a mother suffering from the disease. Other cases reported in infancy were of: lymphosarcoma of the pancreas, described by Eichler (quoted by Dargeon[3]), lymphoblastoma of the intestines,[1] and reticulum cell sarcoma of cervical lymph nodes,[16] and of tibia.[4] One of us (Z.H.Z.) observed reticulum cell sarcoma of the small intestine in a four-year old boy.[18]

The association of *staphylococcus aureus* infection or empyema has been noted in a few cases. Two cases of lymphoma of the lung had staphylococcal empyema, one of which needed decortication.[6] An infant with reticulum cell sarcoma of the tibia first presented as a haematogenous osteitis, and the blood culture was positive for *staphylococcus aureus*.[4] In the present case, it is difficult to say whether the empyema developed in the usual manner from a pulmonary infection, independently of the neoplastic process, or resulted from the infection of the pleural effusion already present as a reaction of the neoplasm. Another possibility, of course, is that infection induced the neoplastic process. This, though not very likely, recalls the view expressed by some earlier clinicians, and discussed by Dargeon.[3]

Since reticulum cell sarcoma is generally radiosensitive, roentgen therapy is still perhaps the most effective treatment. However, the ultimate prognosis is often poor, although a few cases of apparent "cure" have been reported. Many instances of long-term survivals with radio-therapy and/or surgery have been recorded, such as survivals of: 10 years in Bilchick's case (quoted by Stich[14]), 13 years[2,6] and 20 years,[7] in adults; 11 years,[5] and 20 years and three months,[11] in children; and more than five years,[4] without treatment.[7]

The average life expectancy in reticulum cell sarcoma ranges from six to 24 months, with few exceptions. The disease is more aggressive in childhood than in adulthood. The reports of many long term survivals should encourage optimism and enthusiasm.

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Tsutsugamushi Fever Pneumonitis in an American Child in Japan*

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Tsutsugamushi fever, or scrub typhus[1] is a rickettsial disease which is not seen in the United States. It is known variously as mite-born typhus, Japanese river typhus, tropical typhus, and rural typhus. The disease has been known for centuries in Japan, where it occurs chiefly in the Akita, Yamagata, and Niigata prefectures of the northern portion of Honshu Island. The disease has also been reported in the Malay States, the Dutch East Indies, India, Indochina, New Guinea, Guadalcanal, Australia, and New Zealand. The disease was considered to be rare by American workers until World War II, when 6685 cases with 284 deaths were reported among U. S. servicemen; this was in contrast to 64 cases of epidemic typhus with no reported death.[5]

The standard classification of rickettsial disease lists four major groupings: I. the typhus group including Brill's (epidemic) and murine (endemic); II. the spotted fever group; III. tsutsugamushi fever; and IV: miscellaneous grouping, including Q fever. The third, or tsutsugamushi group includes the two etiologic agents of this disease, *Rickettsia orientalis* and *Rickettsia tsutsugamushi*. These organisms, which derive their generic name from the pioneer worker, Howard Taylor Ricketts, are small (.3 — .5 x .2 — .4 mu), diplococcus-like organisms which live as obligate parasites. These organisms show little pleomorphism and appear as purplish dots inside cells. They may be cultured on embryonated eggs and agar.

These organisms are carried by both insects and mammals. They infect the six legged red larvae of the mite of the Trombicula akamushi, Trombicula deliensis, and Trombicula hirsti species. These species of mites are endemic in the lalany and kunai grassfields of the Orient. Rats, fieldmice, and bandicoots serve as mammalian vectors in the life cycle. The disease occurs most commonly from May to December, with the majority of cases seen in the summer months.

The pathology[2] of the disease is based on a disseminated focal vasculitis, an associated perivasculitis, and an invasion of mononuclear cells, including plasma cells, into the involved areas. There is no frank necrosis of the vessel wall, such as characterizes Rocky Mountain Spotted Fever. The maculo-papular rash results from thromboses in the capillary bed. The organs most frequently affected are lung (interstitial pneumonitis and bronchiolitis); heart (interstitial myocarditis); the parenchymatous organs; and brain (mononuclear cell meningitis, glial "nodules," and ganglionic degeneration). There is controversy whether a specific rickettsial toxin or an anergic reaction, such as that hypothesized in the collagen diseases, is responsible for the pathologic changes.

The clinical syndrome is characterized by an incubation period of from six to 18 days, although some authors list 10 days as the minimal period.

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The onset of the disease is marked by headache, fever, and chills. There occurs a sudden increase in fever, to 104° or 105°F (orally), prostration, and evidence of severe and progressive illness. The physical findings at this time reveal only the black eschar which develops at the site of the bite of the tick, and a relative bradycardia, usually between 70 and 100 per minute. Between the fifth and the eighth day of the clinical syndrome there appears the characteristic rash, first appearing as faint red macules which become papular. These usually fade four or five days following their appearance. At the same time erythemata of the mucus membrane may be seen on the soft palate. Conjunctival injection and generalized lymphadenopathy are a prominent part of the picture. During the early stage of the disease cough is a common symptom, occurring in two-thirds of patients; frank pneumonitis is seen in only one-fifth of cases.[5]

The reports of central nervous system involvement[3] are highly variable. Deafness[4] secondary to eighth cranial nerve involvement is the most common manifestation and is seen commonly in the early stages of the disease; it has been reported to occur in as many as 75 per cent of patients during the first few days of illness. Permanent nerve deafness is not common, but has been reported in several cases. Peripheral neuritis, characterized by muscle weakness and sensory deficit, is seen early in the disease; most of these patients, likewise, regain lost function. Other neurological manifestations include anisocoria, coma, convulsions, acute Parkinsonism, and mental disorders. About one-third of patients present with a post-typhus syndrome of lethargy, lassitude, nervousness, and hyperirritability during the convalescent period.

The hematologic and laboratory picture is non-specific, showing an anemia, either a normal or slightly elevated white blood count, reversal of the A/G ratio, and occasional hypochloremic alkalosis, hypofibrinogenemia, and an elevated icteric index.

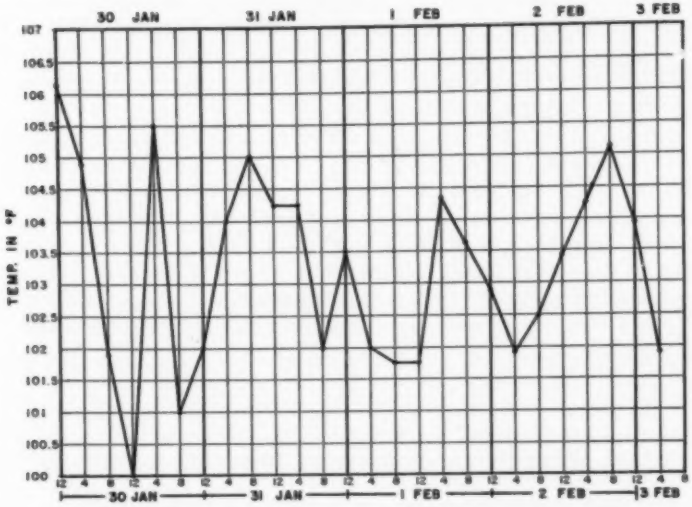

CHART: Fever Chart — January 30 to February 3, 1958.

The diagnosis of the disease is based upon the following criteria: (1) exposure in a geographically endemic region; (2) appearance of a single eschar at the site of attachment of the mite; (3) a clinical syndrome of high fever, conjunctival injection, lymphadenopathy, bradycardia, and a maculo-papular rash; (4) a normal or slightly elevated white blood count; (5) a positive Weil-Felix reaction, showing elevation of the proteus OX-K antibody titer, with no concomitant elevation of the OX-19 or OX-2 titer. This rise begins at the end of the second week of the clinical syndrome and is said to reach its maximum at the end of the third week (a titer of 1/160 is considered diagnostic); (6) rise in rickettsial complement fixation titer; (7) recovery of the rickettsial organisms.

The chemotherapy of this disease has included para-amino benzoic acid, chloramphenicol, chlortetracycline, oxytetracycline, erythromycin and novobiocin. The drug of choice now is chloramphenicol,[6] a rickettsiostatic agent which has reduced the death rate in Japan from 54 per cent to 2.5 per cent.[7] However, one noted authority[8] has expressed reservations about the use of the drug, after his studies indicated that use of this drug inhibited elaboration of antibodies.

The prognosis of the disease varied widely in different geographical regions. In five Japanese prefectures from 1917 to 1948, the mortality rates were 45.8 per cent, 45.3 per cent, 31.6 per cent, 28.6 per cent, and 20.2 per cent. During the same period, the mortality rate was 10.9 per cent in Formosa; 7.7 per cent in New Guinea; and 4.6 per cent in the Philippines. Hara and Abe believe that this difference in mortality reflects the different pathogenicity of the several strains. As has been discussed above, the introduction of chloramphenicol as an agent of treatment markedly reduced the mortality, and now survival is reported in 90 per cent or more of afflicted patients.

Case Report

This four year-old boy, the son of a United States Air Force pilot, had come to Japan from his home in Florida in November, 1957. He had received typhus immunizations in August, 1957. He was entirely well until the day previous to admission,

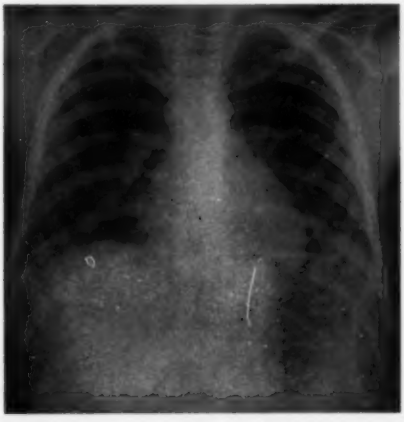

FIGURE 1: X-ray film on day previous to admission: "widespread patchy, nodular, and linear infiltrates throughout both lung fields, suggesting severe acute pneumonitis."

when he developed a low-grade fever and was lethargic and irritable. On the day of admission, he developed a high fever, a macular rash, and began to vomit. He was seen in the hospital dispensary and was given 300,000 units of procaine penicillin and 2 gm. of triple sulfa preparation. His fever continued to rise and generalized convulsions developed. He was brought to the emergency room and admitted to the pediatric ward of the USAF Hospital, Tachikawa, at 2330 hours on January 29, 1958.

At the time of admission, he was seen to be a well-developed and well-nourished boy. The rectal temperature was 106.2°F; the pulse 140 per minute and regular; the respiratory rate 40 per minute and shallow. The child was confused and disoriented. The eyelids were noted to appear "heliotrope." The pharynx was injected. No cervical lymphadenopathy was noted. The chest was clear. Examination of the heart, abdomen and central nervous system were negative. Maculo-papular lesions on the skin of the trunk and extremities were noted. The admission white blood cell count was 9,800 with 77 polymorphonuclears and 23 lymphocytes. The urine was negative. Captain Thomas O. Miller, USAF (MC), the admitting physician, listed: "Acute febrile illness: ? pneumonia, ? Rickettsial disease" as his diagnosis. The child was placed in oxygen, given penicillin, aspirin, and alcohol sponges.

On the following morning (January 30, 1958), the temperature was 100°F. At this time, there was periorbital edema, conjunctival injection, questionable vesication of the tympana, grayish exudate on the tonsils, and "slushiness" of the heart sounds. Later in the day, the rash began to appear vesicular. A lumbar puncture performed at this time was negative. The initial x-ray, made on admission, had revealed widespread patchy, nodular, and linear infiltrates in both lung fields. 100 mgm. Erythromycin and 125 mgm. Chloromycetin q. 6h. were added to the treatment; it was believed that the child had either varicella or staphylococcal pneumonia and septicemia; tuberculosis or deep fungal disease were also suspected.

On February 2, the chest x-ray film revealed hazy density in the right lung fiield and scattered through the left base. There was a suggestion of enlargement of the transverse diameter of the heart and some enlargement of the liver shadow. Congestive heart failure was suspected but not substantiated clinically. Meanwhile, the clinical picture continued to be marked by severe toxicity, spiking fever, pneumonitis with severe dyspnea, and a maculo-papular-vesicular skin rash.

On February 3, Cathomycin, 100 mg. q. 6th. was added. During the next 10 days there was gradual improvement in the clinical picture, with subsidence of febrile spikes, dyspnea, toxicity, and rash. The white blood cell count varied between 6,250 and 11,400, usually with a slight polymorphonuclear cell predominance. There was a moderate anemia. The urines revealed only 6-10 WBC/hpf. Nose and throat cultures revealed no pathogens. Incision and drainage of one of the skin lesions revealed no organisms on culture. Four blood cultures were negative. OX-2, OX-19, OX-K titers drawn on the morning following admission were negative. On February 4, the x-ray film revealed that the infiltrate had spread slightly. However, by February 9, there was marked clearing on x-ray film. On February 11, 1958, the child was discharged with no definite diagnosis.

The Weil-Felix agglutination drawn on the morning following admission revealed negative results in OX-19, OX-2, OX-K series. On February 26, OX-19, OX-2 were negative, but OX-K had risen to 1:160. On March 25, the OX-K titer was positive at 1:320. Subsequently the titer began to fall progressively, although by June 25, it still remained positive at 1:40. Rickettsial complement fixation for Rickettsia tsutsugamushi was reported as positive on serum drawn on March 25, 1958 by the virology laboratory of Tokyo University Medical School.

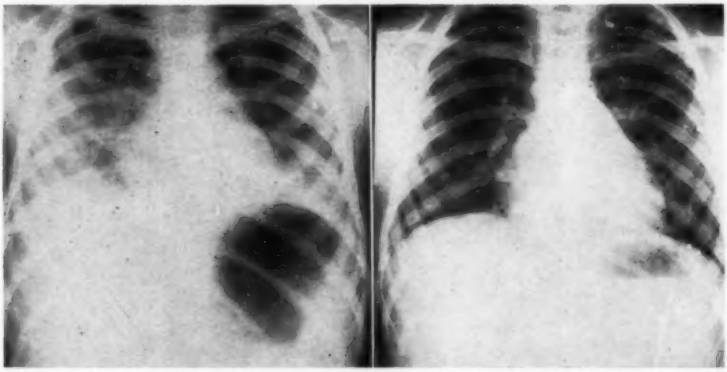

FIGURE 2: On fourth hospital day: "hazy density involving lower portion of right lung field and scattered throughout left base . . . . slight increase in transverse diameter of the heart and liver shadow." FIGURE 3: Two-months follow-up: "considerable clearing continues.

Comment

Considering the criteria for diagnosis listed above, it was felt that this child could be regarded as having had tsutsugamushi fever. Despite the occurrence of the disease outside the epidemic period of the year and in a region of Japan outside the endemic area (although tsutsugamushi fever is not rare in the Tokyo-Kanto plain region, where USAF Hospital, Tachikawa, is located), it is felt that the clinical and laboratory picture support this diagnosis. Despite a vigorous search, no escher was found; but the clinical syndrome was marked by the characteristic high fever, conjunctival injection, lymphadenopathy, and maculo-papular rash. Bradycardia was not present. The white blood count was typical for this disease. The OX-K titer showed a diagnostic rise, with no associated rise of the OX-2 and OX-19 antibodies. The rickettsial complement fixation test was positive. The failure to recover rickettsial from the blood may have reflected the unfamiliarity of our laboratory personnel with the techniques necessary for isolation.

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The President's Page

THEY ALSO SERVE.

A little more than a quarter of a century ago, a small group of medical men of initiative, intuition, inquisitiveness, and daring, concurred in the idea that there was need for a scientific organization dedicated to diseases of the chest. This was to be an international organization. It was to include not only diseases of the lungs but also of the heart.

When the plan was first broached, opposition, prejudice, hostility and ridicule was encountered, and had to be overcome before it was possible to successfully establish the American College of Chest Physicians. Strong conviction and broad perspective triumphed, however, and enthusiastic and constructive efforts supported this new departure. Foresighted founders of the College emphasized that the aims and purposes of this organization were far more inclusive than a campaign against a single disease. It was emphasized that all measures toward the conquest of tuberculosis would be sustained by the untiring and full support of the entire membership. At the same time, attention was directed to the prevalence of non-tuberculous diseases of the lungs, congenital and acquired heart diseases, and ailments of other thoracic organs and structures.

Pioneers of the College insisted on an attack on a broad front, for the reason that diseases of the chest have been attacking the human body on a broad front since the dawn of history. To forget or to underestimate non-tuberculous afflictions of the lung and non-tuberculous pathological conditions in other parts of the chest, would have been gross oversight, inexcusable dodging of responsibility as chest specialists, or what one might perhaps term "malfeasance" in the practice of medicine.

Fortunately, through indefatigable perseverance, through methodical organization efforts, through aggressive action and with men of leadership at the helm of the newly organized College, and with the help of an interested, loyal membership, this organization became solidly established. Judging from the progress of the last 26 years, it is here to stay.

This world-wide scientific body is recognized today by the medical profession of many countries as the champion of scientific progress, medical education and research as it pertains to diseases of the heart and lungs. Moreover, the American College of Chest Physicians occupies a prominent position among organized specialty groups in the United States as well as in other countries.

The principles, ideals and endeavors of the American College of Chest Physicians have prompted outstanding chest specialists the world over to join its ranks and to contribute actively to its further development. It is now realized that by strengthening the College, advancement of medical science is thereby strengthened.

With this precept in the minds of all of our members, we can be confident of continued devoted and faithful cooperation, and collaboration of the entire organization.

Thus, let us look forward with justifiable hope and conviction, to ever-increasing achievements by the American College of Chest Physicians. All physicians interested in diseases of the heart and lungs will find in the College a vehicle for further education and development.

CHAPTER NEWS

SOUTHERN CHAPTER

The 17th annual meeting of the Southern Chapter of the College will be held at the Statler Hilton Hotel, St. Louis, Missouri, October 30 and 31. The Chapter, which encompasses all the southern states, will meet in conjunction with the meeting of the Southern Medical Association. Following is the chapter program:

October 30 — Morning Session

9:00 a.m. "Tuberculosis in an Industrial Plant"
J. T. Perret and N. K. Weaver, Baton Rouge, Louisiana

"Adrenocorticoids in the Treatment of Tuberculosis"
W. W. Coulter, Jr., Lafayette, Louisiana

"Adult Histiocystosis: Report of Ten Cases with Emphasis on Pulmonary Findings"
John N. Bickers and Perry J. Eckman, New Orleans, Louisiana

"Physiologic Studies on Patients with Bullous Emphysema"
Charles E. Andrews and William Ruth, Kansas City, Kansas

"Hypertrophy of the Right Ventricle in Centrilobular and Panlobular Emphysema"
Herbert C. Sweet, James R. Wyatt and Peter Kinsella, St. Louis, Missouri

"Spontaneous Pneumothorax"
Mark W. Wolcott, W. A. Shaver and W. D. Jennings, Coral Gables, Florida

Afternoon Session

1:20 p.m. "Diagnosis and Management of Pleural Disease—An Analysis of 200 Cases"
M. N. Atay, J. L. Yates, H. V. Langeluttig and C. A. Brasher, Mt. Vernon, Missouri

"Early Signs and Warnings of Coronary Disease"
Edward Massie, St. Louis, Missouri

"Controversial Aspects of the Management of Symptomatic Coronary Atherosclerosis"
Thomas M. Blake, Jackson, Mississippi

"Anomalous Vascular Patterns Found with Atrial Septal Defects"
Robert H. LePere, San Antonio, Texas

"Congenital or Acquired Absence or Hypoplasia of One Pulmonary Artery"
Milton V. Davis, Maurice Adam and Ben F. Mitchel, Jr., Dallas, Texas

Seventh Annual Paul A. Turner Memorial Lecture
"Role of Angiography in the Management of Pulmonary Disease"
Osler A. Abbott, Atlanta, Georgia

October 31

9:00 a.m. "Correlative Studies of the Effect of the Varied Protein and Caloric Intakes and an Anabolic Steroid on Metabolism following Pulmonary Surgery"
Watts R. Webb, Richard S. Doyle and Hector S. Howard, Jackson, Mississippi

"Diagnosis and Management of Mediastinal Tumors"
DeWitt C. Daughtry, Miami, Florida

"Management of Metastatic Malignant Lung Disease"
Charles L. Roper, St. Louis, Missouri

"Experiences with Emivan, A New Respiratory Stimulant"
George L. Baum, C. Hagedorn, I. N. Rosenstein and S. Silipo, Coral Gables, Florida

"Clinical Repercussions from Healed Histoplasmosis"
Joseph W. Peabody, Jr., Sol Katz and Edgar W. Davis, Washington, D.C.

"Is There A Relationship between Histoplasmosis and Silicosis?"
Willie Cortez, J. L. Yates, H. V. Langeluttig, C. A. Brasher, Mt. Vernon, Missouri; and Michael L. Furcolow, Kansas City, Kansas

12:15 p.m. Luncheon and business meeting

Guest speaker: Herman J. Moersch, Rochester, Minnesota, Director of Medical Education and Research, American College of Chest Physicians

MICHIGAN CHAPTER

The fall meeting of the Michigan Chapter will be held at the Sheraton-Cadillac Hotel in Detroit, September 28, in connection with the annual meeting of the Michigan State Medical Society. The scientific program will consist of the following:

4:30 p.m. "Physiology of Pulmonary Diffusion in Occupational Diseases"
Arthur J. Vorwald, Detroit

"Bronchogenic Carcinoma"
William A. Hudson and Clyde K. Hasley, Detroit

"Chemotherapy in Tuberculosis"
James T. Cheng, Pontiac and W. L. Howard, Northville

"Coronary Disease and its Treatment"
Norman E. Clarke and James Fryfogle, Detroit

Dinner will be served following the scientific session.

New officers of the Michigan Chapter, elected at the chapter meeting in Detroit, April 21, are:

President—James T. Cheng, Pontiac

Vice President—Arthur J. Vorwald, Detroit

Secretary-Treasurer—John L. Isbister, Lansing

VIRGINIA CHAPTER

Dr. G. W. H. Schepers of Wilmington, Delaware will speak on "Pulmonary Changes Incident to Occupational Exposure to Fumes, Gases and Dust" on October 10 at Virginia Beach, Virginia. Dr. Schepers has been selected to represent the Virginia Chapter at the Medical Society of Virginia Meeting.

INDIANA CHAPTER

The annual meeting of the Indiana Chapter will be held at the French Lick Hotel, French Lick at 12:00 noon on October 5. Guest speaker at the luncheon meeting will be Dr. John D. Miller of Indianapolis who will present the subject "Changes in Medical Problems of the Sanatorium."

SOUTHERN CHAPTER OF SOUTH AFRICA

The annual meeting of the Southern Chapter of the Union of South Africa was held in Cape Town on May 2. Dr. Hendrik Muller of Cape Town, chapter secretary, reported that seven scientific sessions had been held during the year, four of which included papers presented by speakers who were especially invited to lecture on their latest work. Dr. W. Silber spoke on "Benign Conditions of the Lower Esophagus," Dr. G. Efron presented a paper on "Carcinoma of the Thoracic Esophagus," and Dr. Ite Boerema of the University of Amsterdam spoke on "Esophageal Varices." One meeting was devoted to a Symposium on Asthma and its Treatment, including the Allergic, Psychiatric and Surgical Aspects." A special panel from the University of Cape Town participated in this symposium.

The following chapter officers were re-elected:

President—David P. Marais, Cape Town

Vice President—Theodore Schrire, Cape Town

Secretary—Hendrik Muller, Cape Town

Treasurer—Michael Bailey, Cape Town

MINNESOTA CHAPTER

The annual meeting of the Minnesota Chapter was held at Gull Lake in Brainerd, July 9-10. At the close of the scientific session, the following officers were elected:

President—Josiah Fuller, Duluth

Vice President—W. Robert Schmidt, Minneapolis

Secretary Treasurer—Coleman J. Connolly, St. Paul (re-elected)

BOOK REVIEW

THE CONQUEST OF BOVINE TUBERCULOSIS IN THE UNITED STATES, by Howard R. Smith, Somerset, Michigan, price, $1, Order direct from author.

This volume of less than 100 pages is an account of the most phenomenal accomplishment in tuberculosis control ever achieved among animals or people in a major nation population-wise.

Table 3 of this book shows the effectiveness of the program. In 1917, of the 9,276,049 market cattle slaughtered, the carcasses of 8,418 had to be sterilized as unfit for food and 40,756 were condemned because of tuberculosis; whereas in 1957, of the 20,141,371 market cattle slaughtered, the carcasses of only 16 had to be sterilized and only 196 condemned. This is 99.7 per cent decrease in proportion to number slaughtered. Among the 95,000,000 cattle in the United States, during the fiscal year 1957, testing with tuberculin revealed that only 0.156 per cent were harboring tubercle bacilli.

In a most fascinating way, H. R. Smith, Doctor of Agriculture, tells how this accomplishment was achieved. In 1912, as Head of the Department of Animal Husbandry at the University of Nebraska, Doctor Smith transferred to the Chairmanship of the Department of Animal Husbandry at the University of Minnesota. In 1915, he became livestock specialist for the organizations which James J. Hill, St. Paul, represented including the Great Northern Railroad and the First National Bank of St. Paul. In 1917, he became Livestock Commissioner for the market interests in Chicago to devote his entire time to educational and promotional activities to initiate and help carry on a national campaign to eradicate bovine tuberculosis. In 1934, he was appointed General Manager of the National Livestock Loss Prevention Board and held this position until retirement in 1951. In the early years of his career, tuberculosis was the most destructive disease among the cattle of this country.

In this volume, he tells how the bovine type of tubercle bacillus entered the United States and spread to such serious proportions. His first experience with it was as a student at the Michigan Agricultural College (now Michigan State University) in 1894 where pioneer work with the tuberculin test was being done. He observed this test to be so specific that wherever he worked thereafter, he insisted upon its use. He spent a great deal of time in Washington testifying before legislative committees on the importance of adequate appropriations for the eradication of tuberculosis among animals. Indeed, he played an exceedingly important role in procuring the first large federal appropriation for this purpose. He then worked diligently with state legislators in order that each state match the federal offering before it could be granted.

Despite the intense opposition to the tuberculosis eradication program by uninformed, misinformed, or selfish individuals, Dr. Smith worked unceasingly to see that accurate information reached owners of cattle, legislators and all others concerned.

Tuberculin testing of cattle was placed on a county-wide basis. The reactors were removed and periodic testing done until all of the 3,072 counties of the United States received the modified accredited rating. This rating was awarded the counties as fast as the incidence of tuberculin reactors reached 0.5 per cent or less. Ever since, periodic tuberculin testing has been continued with the eradication of the bovine type of tubercle bacillus as the goal. This has been attained in many places where no animal reacts to the tuberculin tests. However, in the nation as a whole, about 0.15 per cent of the animals react. There is evidence that many of these acquire their infections from owners, farm hands, and other human contacts who have contagious tuberculosis.

This book also calls attention to how the control of tuberculosis among cattle reduced the disease among people. Prior to 1917, a large number of people acquired tuberculosis from cattle. There is evidence that an important block of the incapacitating and killing disease of that period among people was due to the bovine type of tubercle bacillus. Now infection of people from cattle has almost ceased to occur.

In 1917, Dr. John A. Kiernan, then Chief of the Division of Tuberculosis Eradication of the United States Bureau of Animal Industry, was asked how long it would take for the nation-wide eradication of tuberculosis campaign to solve the problem. He wisely answered that there was no ground upon which a reasonable estimate could be made. He said, "All one can do is to make a guess as to the time, and it is my belief that if this nation succeeds in eradicating tuberculosis in 50 years, it will be one of the greatest heritages our successors will have handed down to them." If the eradication methods of the past are continued and intensified, it seems probable that by the time the 50 years has passed in 1967, the bovine type of bacillus will have been eradicated from cattle. However, unless drastic action is taken to administer the tuberculin test to people everywhere, examine the reactors and keep them under obsrvation as Dr. Smith recommends, there will still be tuberculin reactors among cattle caused by infections transmitted by humans.

The remaining problem to be solved both among animals and people will be the responsibility of members of 4-H clubs and Future Farmers of America to whom this book is so wisely dedicated, as well as every present and future American youth. The book is an accurate accounting step by step of a method applied with such success that it has been designated man's greatest victory over tuberculosis. With appropriate modifications, it can be made as effective in eradicating tuberculosis from people.

Physicians everywhere can contribute significantly in the program of eradication of all types of pathogenic tubercle bacilli by contacting leaders of 4-H clubs and Future Farmers of America in an endeavor to place Dr. Smith's book in possession of every member.

J. Arthur Myers, M.D.

CALENDAR OF EVENTS

National Meetings

Interim Session
American College of Chest Physicians
Washington, D.C., November 26-28, 1960

27th Annual Meeting, American College of Chest Physicians
New York City, June 22-26, 1961

Postgraduate Courses

15th Annual Course, Clinical Cardiopulmonary Physiology
Chicago, Illinois, October 24-28, 1960

13th Annual Course, Recent Advances in Diagnosis and Treatment of Diseases of the Heart and Lungs
New York City, November 14-18, 1960

Chaper Meetings

Michigan Chapter, Detroit, September 28
Indiana Chapter, French Lick, October 5
Virginia Chapter, Virginia Beach, October 10
Southern Chapter, St. Louis, October 30 and 31
Pacific Northwest Chapter, Seattle, November 11-12